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HEALTH ASPECTS OF CASTOR BEAN DUST: REVIEW AND BIBLIOGRAPHY

Edwin M. Apen, Jr., et al

National Center for Air Pollution Control
Cincinnati, Ohio

1967

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Review and Bibliography

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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

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HEALTH ASPECTS OF CASTOR BEAN DUST

Review and Bibliography

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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Bureau of Disease Prevention and Environmental Control

Cincinnati, Ohio

1967

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ABSTRACT

Castor pomace is the residue that remains after castor oil has been removed from the beans of the castor plant *Ricinus communis*. It is initially in flat cakes, which are broken up into a fine dry powder. This pomace contains one of the most potent allergens known. It is, therefore, of considerable interest in occupational medicine. Severe allergic reactions frequently occur in exposed workers when appropriate safeguards are not employed. In addition, the fine, light powder form in which the pomace occurs is readily transported from factory and shipping areas into the surrounding community by winds. As a community air pollutant, the pomace can cause widespread and severe allergy in the neighborhoods of mills and factories where it is produced or handled. This publication reviews the occupational and air pollution aspects of castor pomace. An annotated bibliography and selected translations of foreign articles are also included.

HEALTH ASPECTS OF CASTOR BEAN DUST

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INTRODUCTION

The dangers as well as the benefits to man and animals inherent in the castor plant have been known for many years. The Public Health Service has been particularly concerned with the problems arising from the commercial uses of this plant. Studies have been conducted by the Division of Occupational Health on industrial exposure and illness. The Division of Air Pollution has been interested in the nonoccupational epidemics of allergic asthma that occur occasionally in the vicinity of factories that handle castor plant material. In both Divisions of the Public Health Service the pertinent literature was carefully accumulated and studied. This publication presents material considered useful and valuable in investigating these and similar occupational health and air pollution problems.

The first section of this publication is a review of the work done by various scientists in a number of countries. This is followed by the bibliography. Since the literature on castor plant problems is

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more extensive than that on other commercially used pathogenic plants, it seemed useful to include abstracts with the titles and, in a few instances, to use extensive quotations where the original material is of considerable interest but not readily available. The bibliography is, we hope, complete in its coverage of reports on occupational and community illnesses caused by the castor plant. Other aspects of this interesting plant are represented by selected references only. The final section consists of complete translations of six papers, originally published in less common languages, that contain considerable information on occupational and/or community illness in several countries.

REVIEW

REVIEW

Agricultural and Commercial Aspects

The castor plant (Figures 1 and 2) *Ricinus communis* is a native of tropical Africa and Asia. It is now found in most tropical and subtropical areas and in some temperate areas. The larger varieties (up to 12 feet in height) are widely used as ornamentals. Smaller kinds are extensively cultivated as a commercial crop. Medical interest in the plant is of long duration. For over a century the oil extracted from the beans has been valued as a safe and efficient cathartic.

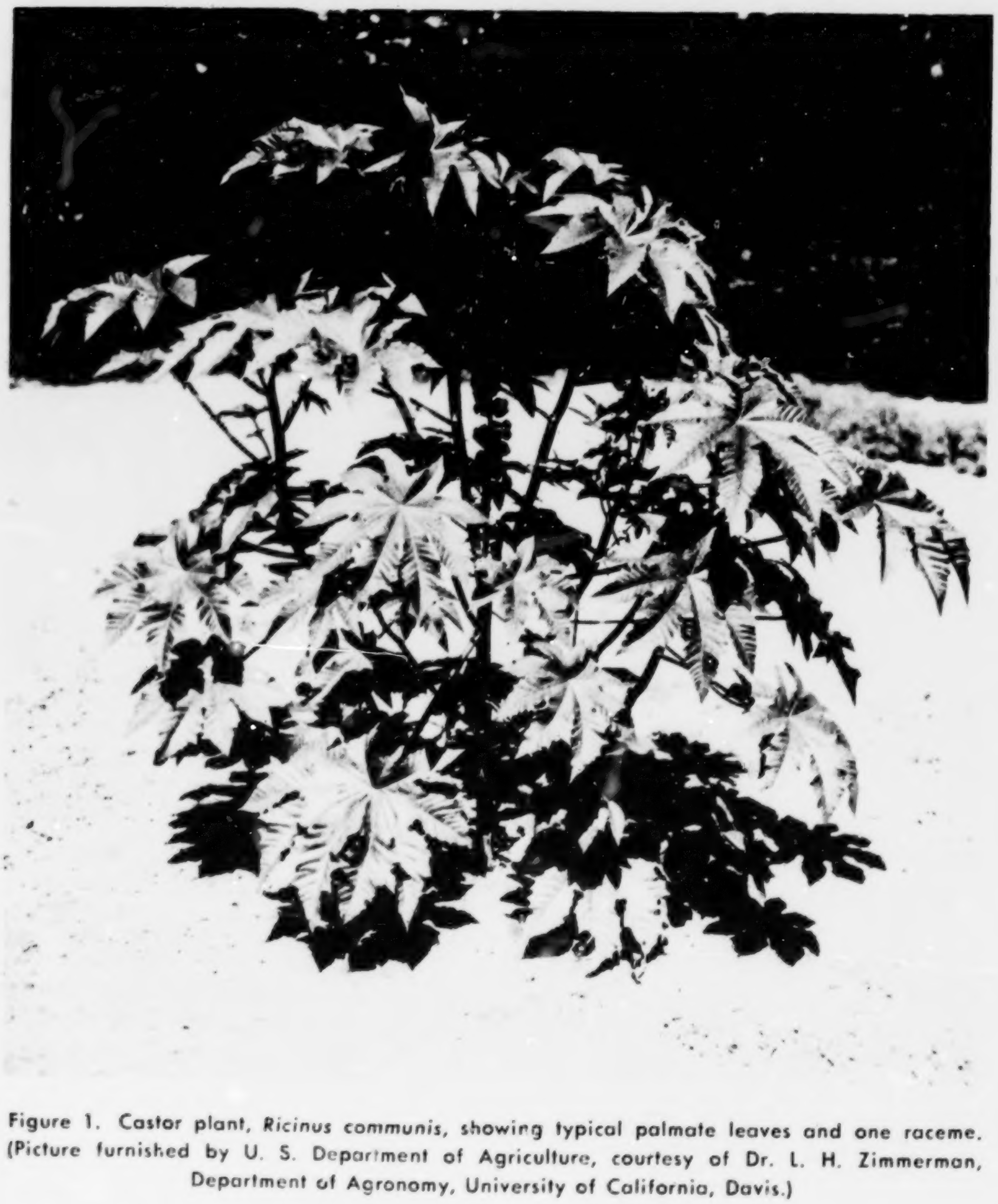

Figure 1. Castor plant, *Ricinus communis*, showing typical palmate leaves and one raceme. (Picture furnished by U. S. Department of Agriculture, courtesy of Dr. L. H. Zimmerman, Department of Agronomy, University of California, Davis.)

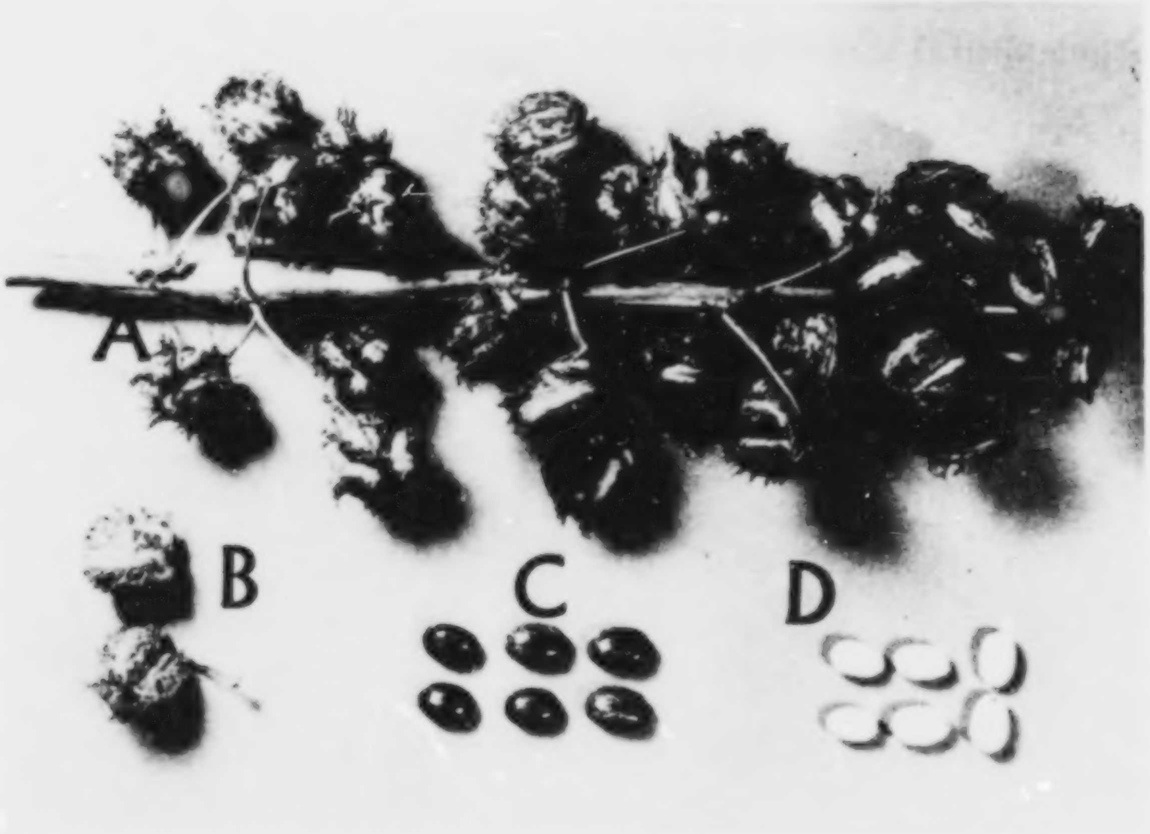

Figure 2. Castor plant. (Material for photograph was furnished by Dr. L. H. Zimmerman, Department of Agronomy, University of California, Davis.)

A. Raceme or "spike" of *Ricinus communis*, with approximately 40 mature seed pods.

B. Two seed pods, each with three seed-containing carpels.

C. Castor seeds from two seed pods, after removal of hull or capsule, but with seed coats intact.

D. Seed kernels after decortication.

In more recent years other commercially valuable properties of the oil have been recognized. This has caused an increased demand for the oil, and hence an increased production. Castor oil, when placed under vacuum and heated with a catalyst, gives up a molecule of water creating conjugated double bonds. Such oil is used for paints, varnishes, and lacquers; its derivates are used in plastics, rayon, nylon, asphalt tile, fungicides, rubber products, soaps, imitation leather, and lubricants. It is used in hydraulic fluids, all-purpose grease, and combat wire, and as a plasticizer in fabrics and explosives. In many instances it serves as a drying agent. It is particularly valuable for hair tonics, lipsticks, and salves.

Castor bean was essentially a wild tropical plant until 50 years ago. As a result of the demands for castor oil during the first World War, commercial plantation production was instituted, and the beans were harvested and handled in large quantity. Plant breeding and strain selection extended the crop into the warm temperate zones, and harvesting machinery and commercial processing equipment have been developed.

Castor oil is extracted from the beans of the plant by pressing. This removes from 70 to 90 percent of the oil. Further extraction of most of the remaining oil may be accomplished by treating the pressed residue with fat solvents. Chemical extraction, a more recently introduced process than simple pressing, is characteristic of large scale production (Figure 3). The residue remaining after the oil is extracted consists of a crushed and very finely divided vegetable powder. This has been called pulp, bran, dust, pomace, meal, etc.* When only pressure is used to extract the oil, the pomace is somewhat oily. When pressure is followed by chemical extraction, the pomace is very dry and is easily dispersed by slight air motion.

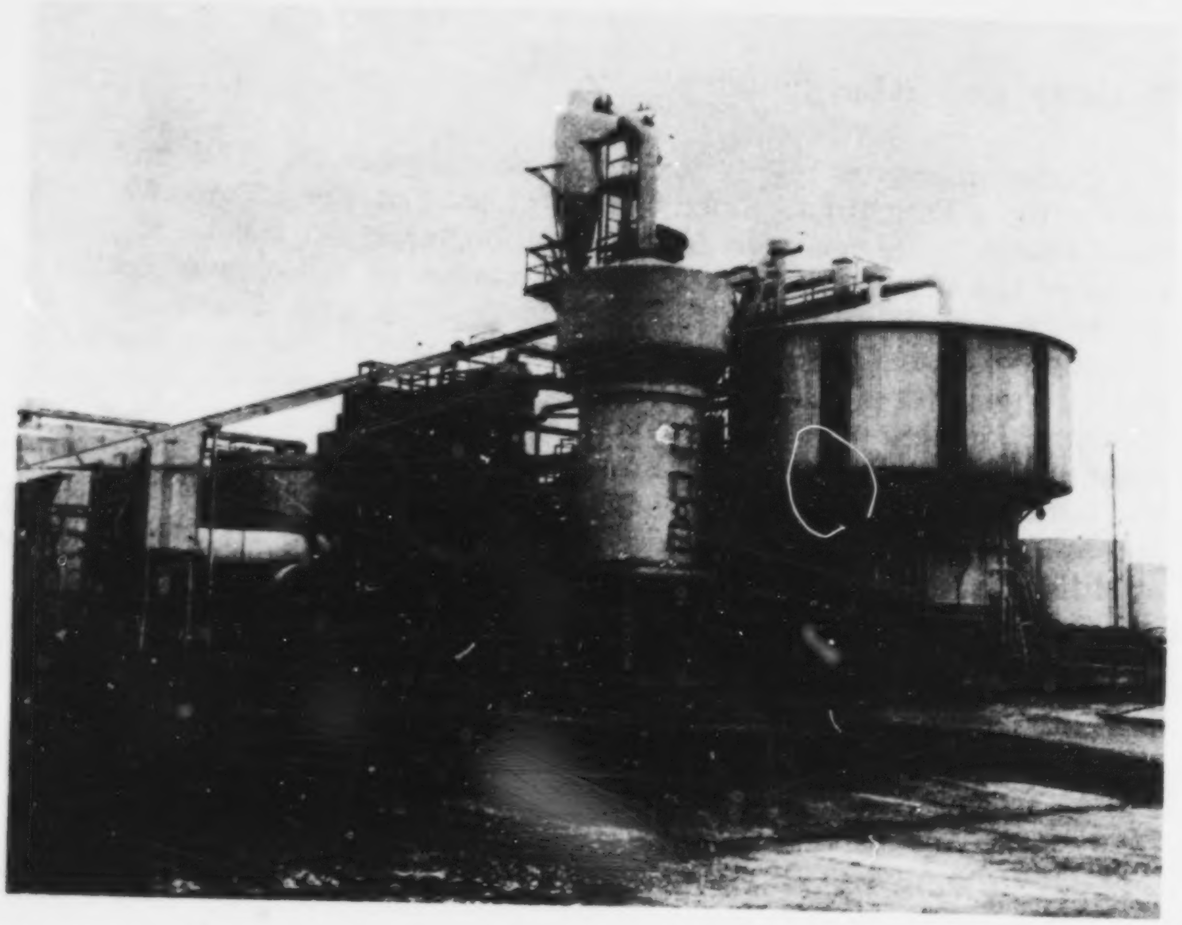

Figure 3. Solvent extraction plant for castor oil manufacture. (Pacific Vegetable Oil Corp., Richmond, Calif.)

The bean is composed of about 50 percent oil and 20 percent protein. The defatted pomace is valuable chiefly for fertilizer. It can be used for animal feed when detoxified but has certain inadequacies in this respect, e.g., lack of essential amino acids. A synthetic fiber created from the protein has no advantage over synthetic fibers from other plants. The enzyme ricinous lipase found in castor pomace has industrial application in defatting processes and is of some interest from a purely chemical point of view. Ricinine, a mildly toxic alkaloid, and phytin are also found in castor pomace. The remainder of the pomace consists of small amounts of water, carbohydrates, and fiber.

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* In this review the term pomace will be used.

Extended discussions of the material briefly reviewed in the preceding paragraphs can be found in several of the articles in the bibliography. For consideration of the agricultural aspects, attention is particularly directed to Zimmerman(*127*). Present and potential uses of castor plant products, and manufacturing aspects are discussed in Bolley and Domingo(*10*), Bolley and Homes(*11*), Jones(*62*), McIntyre(*88*), and Small(*112*). The latter report is written from a medical viewpoint.

Toxicity and Allergenicity

Castor beans are highly toxic to man and animals. This has been known for a long time. Since the latter part of the nineteenth century, considerable research has been undertaken on the toxic properties of the bean and pomace. In the course of these investigations another injurious property, that of allergenicity, was discovered. At first these two were confused. Eventually it was shown that the toxic and allergenic properties were due to separate substances present in the plant, which were particularly concentrated in the bean and pomace. Other oil seeds are known to have similar properties(*120*), but both toxin and allergen of the castor plant are among the most potent known. They have, therefore, merited and been given more attention than similar substances derived from other plants.

As pointed out in other sections of this review, after the oil has been expressed or extracted from the castor bean, about 50 percent of the bean (by weight) remains as castor pomace. Castor oil, commercially the most valuable product of the castor bean, is not a hazardous material in commerce. Idiosyncratic reaction to it when given medicinally is rare. Only one case of sensitivity has been reported(*9*). The pomace, on the other hand, is toxic.

Ricin is the major toxic component of castor pomace. It is an albumin, intermediate in toxicity between the most potent bacterial exotoxins (e.g. botulinus toxin) and the toxic alkaloids, and is capable of killing guinea pigs and rabbits in intravenous doses as low as 1 microgram per kilogram. Its mechanism of action is still imperfectly understood(*17, 18, 19, 50, 92*). It is not only hemorrhagic to highly organized species, inducing multiple capillary hemorrhages, but is also toxic to single-celled organisms. In man, lethal doses produce nausea, vomiting, diarrhea, tenesmus, abdominal cramps, and hemorrhagic changes in the gastro-intestinal tract; ricin produces intense eye irritation also.

The agglutination of red blood corpuscles is a property of ricin, and the hemagglutination test has often been used as a rough assay of the ricin content of pomace. Enzymatic and immunologic studies, however, have shown that the agglutinative and toxic properties in castor pomace are independent. The toxic property is destroyed by boiling, whereas the agglutinative property is lost at a lower temperature(*37*). Toxicity tests, therefore, in lower animals are needed for meaningful assays(*30*).

Ratner and Gruehl(*102, 103, 104*) demonstrated that the inhalation as well as intraperitoneal or intravenous injection of castor pomace would kill guinea pigs. They differentiated deaths due to anaphylaxis. Deaths from ricin occurred several hours after a single exposure, and the hemorrhagic changes involved various abdominal viscera and the lungs. Anaphylactic reactions, on the other hand, occurred immediately after a second or later exposure whenever a suitable incubation period had elapsed, and the pathologic changes were distinctive. These authors also demonstrated that repeated exposures of the animals to pomace produced relative immunity to ricin but sensitization to the allergens. This development of immunity was consistent with the earlier findings of Ehrlich(*47*) who first demonstrated that ricin was capable of producing active immunity. Ratner and Gruehl postulated that humans repeatedly exposed to castor pomace probably escape ricin poisoning because of the development of such immunity. Although epidemiologic evidence of this is not impressive, it is likely that varying levels of immunity and sensitivity, as well as dosage factors, explain some of the variations that are seen in clinical and epidemiologic patterns.

The clearest differentiations of the effects of ricin and castor allergen and their relations to each other are probably those made by Cannan et al.(*15, 16*) and Corwin et al.(*31*) and discussed by Corwin(*36, 37*). They are fundamentally in agreement with the concepts discussed above. Similar findings and conclusions were made by Matsui et al. in studies recently carried out in Japan(*87*).

Unlike the toxin, the allergenic substance (or substances) of the castor plant has no name to distinguish it. The presence of such a sensitizing property in the plant was first demonstrated in animals by Schern(*109*). It was later shown in man by Borchardt(*12*) and Alilaire(*1*), who observed their own sensitivity to castor pomace. They assumed that the toxic and allergenic substances were identical, whereas later work has shown them to be separate.

Grabar and Koutseff(*55*) in 1934 showed that (a) the seeds and the bean cake both contain ricin and allergen; (b) the ricin is thermolabile, whereas the allergen is heat resistant; (c) the ricin is precipitated by ammonium sulfate; and (d) the ricin is not dialyzable, but the allergen is. For their experiments(*55, 56*), they used the commercial castor cake after the oil was extracted. The method of Osborne et al.(*95*) for preparing ricin was first employed. Simple boiling and dissolving in absolute alcohol isolated the allergen in quantity.

Coulson, Spies, and coworkers began their important investigations(*38, 42, 115, 121*) on the physical, chemical, and physiological properties of oilseeds in 1940 when they isolated the cottonseed allergen. They suggested the name "natural proteose" for the protein allergen. In 1943(*116*) they isolated a nontoxic allergenic protein polysaccharide fraction, CB-1A, from castor beans by the procedure used for cottonseed. CB-1A represents 1.8 percent of defatted castor pomace; its properties are similar to those of cottonseed allergen, but it contains no tryptophane. Minimal shocking and sensitizing doses were determined for CB-1A. It is immunologically distinct from other antigens of castor bean, and exceedingly small amounts produce positive passive transfer tests.

In 1944 Spies et al.(*121*) showed that the CB-1A allergen fractions of domestic and of Brazilian castor pomace are immunologically equivalent. They(*119*) also isolated an essentially carbohydrate-free allergenic protein, CB-65A, from the CB-1A fraction of castor pomace and showed that the chief allergenic and anaphylactogenic specificities of CB-1A are inherent in the carbohydrate-free protein fraction, CB-65A. (See also Layton et al.(*71*).) The carbohydrate portion of the allergenic fraction plays no role in determining immunological specificity(*42*) or shocking capacity of the protein, but does influence the capacity to induce antibody formation. It also enhances the anaphylactogenic capacity of the allergenic protein.

Layton et al.(*67, 82*) in recent years demonstrated not only that several allergens are present, but also that allergens are in pollen and other debris associated with castor beans and that cross-reactions occur with closely related plant species(*80*). These cross-reactions may explain the sensitivity in some individuals with no known prior contact with castor beans. They have also investigated the suggestion of Freedman, Siddiqi, and others(*52, 53, 110*) that chlorogenic acid is an allergen common to castor beans and other plants. The studies of Layton et al. on this subject(*70, 72, 78*) indicate that the previous results of Freedman et al. were due to allergenic impurities in the chlorogenic acid employed.

Although the allergens are quite heat stable(*53, 117*), pomace samples from different methods of production vary widely in allergen content(*41*). For example, some steam-treated material has 1/40th the CB-1A content of nontreated pomace. Solvent extraction results in a dry, dusty residue, which is a greater environmental hazard than the oilier meal that results from simple expression(*89, 94*). Steam treatment for solvent recovery has been shown to reduce toxicity markedly and also to diminish allergenicity. Thus different pomaces vary in their potential biologic effects, but none now commercially available are completely free of toxicity and allergenicity(*30*).

Corwin et al.(*31*) have emphasized the great importance of particle size in relation to the effects of castor pomace. Difficulties rapidly increase with the decrease in the size of the particles being produced or handled.

Clinically, the pattern of illness found in both industrial and community exposures is dominated in most instances by the effects of the allergen. The symptoms characteristically are those of allergic conjunctivitis, rhinitis and asthma. Itching and tearing of the eyes, nasal itching and discharge, paroxysmal sneezing, and tightness of the chest and wheezing (which in severe cases proceed to status asthmaticus) constitute the symptom complex. The frequency with which urticaria is observed is noteworthy. In some outbreaks nearly 50 percent of the patients have skin lesions, and 25 percent is a common proportion. These skin lesions are often described as affecting mainly the exposed skin surfaces, but this is not always the case.

As pointed out earlier, nonimmune individuals heavily exposed to pomace that has not been partially detoxified may show symptoms of ricin intoxication after the inhalation and concurrent ingestion of sufficient ricin to produce illness. Although the ingestion of whole castor beans(*3*, *21*) is not an unusual cause of fatalities, we know of no reported deaths from human inhalation of pomace. Nevertheless, if the clinical picture is dominated by nausea, vomiting, abdominal pain, headache, and fever, the possibility of ricin as a factor should be considered(*30*, *97*, *103*).

The clinical diagnosis of the allergic reaction can usually be made from the symptoms, but in the presence of an outbreak, symptoms of psychogenic origin can be confusing. Eosinophilia commonly accompanies identified cases; Lupu et al.(*84*, *85*)found above 5 percent eosinophiles in 72 percent of symptomatic cases. Thus, etiologic diagnosis depends upon first suspecting castor beans as a possible factor and then establishing this by a history of possible exposure. Challenging the patient with castor bean allergen by skin test is useful, but it requires appreciation of the risk of severe allergic reaction and of the fact that crude castor bean extract contains ricin as well as allergens. The allergens used have varied from whole extracts of castor pomace (which should be detoxified with heat to eliminate ricin) to more refined allergens such as the CB-1A developed by Spies and Coulson(*116*). Competent allergists repeatedly stress that only scratch tests should be used and that intradermal testing is dangerous. Many authors have commented on the violent reactions that may occur from the skin test and have indicated that preliminary testing with an extremely dilute preparation is essential. Layton et al.(*76*) used a 1:2,000,000 dilution of CB-1A for their initial trial.

The Prausnitz, Kustner test, or the passive transfer of reagins to the skin of human recipients with subsequent local challenging with the allergens under consideration, is a highly specific test procedure. It involves some slight risk to the recipient in that there is always the possibility of transferring viral hepatitis. Recently, monkeys(*69*, *74*, *81*), lemuroids(*68*), other anthropoid species(*73*), and guinea pigs (*75*) were shown to be feasible for such testing by the passive cutaneous sensitization or allergic serum transfer (AST) test of Layton et al.(*74*). The AST test is a valuable experimental tool and is useful in diagnosis(*76*).

The exposure of individuals to castor pomace under experimental conditions has been used diagnostically with dramatic results in a number of studies. It is not, however, recommended as a routine diagnostic procedure. There are no specific procedures for the diagnosis of ricin poisoning other than by means of the symptom complex. Various immunologic tests could undoubtedly be applied, but the literature contains no references to their clinical use. Patients with allergic symptoms respond well to antihistaminic and bronchodilator drugs, and their treatment does not differ from that given for other types of acute allergy.

Occupational Illness

The highly toxic and allergenic nature of the castor bean has been adequately documented in many areas where this plant is either a native plant or a commercial crop. In the growing, harvesting, transporting, and commercial processing of the beans, whenever they have been handled in quantity, serious and incapacitating reactions have occurred in some of the individuals engaged in the daily operations of production and processing.

Approximately 50 articles in the world's scientific literature during the past half century contain descriptions of illnesses attributed to castor pomace. The authors report in varying detail the toxic or allergic reactions of over 1,500 individuals whose exposures occurred while raising or harvesting castor beans, producing castor oil, handling beans or castor pomace during shipment, manufacturing or using fertilizers, working or living near oil mills or fertilizer plants, or merely being in contact with sacks or other containers contaminated with castor bean products. Thus, the potential risk in excessive or intermittent exposure to castor beans or their residues has been demonstrated amply. The actual hazard in any given situation is dependent upon a great number of factors and requires an understanding of the complex nature of the hazardous components and their biologic effects, and how these may be modified.

The chief source of these problems is the handling of the dry castor pomace after the oil has been extracted, but incidents have been recorded where sensitization to leaf dust, hulls, and pollen may have been the cause of the reaction. The following discussion points out a few of the references found valuable in elucidating the nature of the reactions observed and in illustrating the similarities found in various areas of the world where the reactions have been observed and reported.

The first reports of the reactions to castor pomace were made by those who were studying castor beans and their products in the laboratory. Borchardt in 1913(*12*) described his own case of hay fever and asthma from such laboratory exposure. The following year Alilaire(*1*) related that he had experienced rhinitis, asthma, and urticaria while working with castor beans. The first documented occupational illness in the United States was that reported by Bernton in 1923(*6*); he described rhinitis and asthma in a laboratory chemist of the Department of Agriculture. Robbins(*106*), Kraus(*66*), Jacoby (*60*), Snell(*114*), Follweiler and Haley(*51*), Woringer(*123*, *124*), Woringer et al.(*125*), and Buton(*13*) subsequently recounted similar isolated occurrences in laboratory workers. Diagnoses were usually based upon the history of contact, although Bernton(*7*) obtained positive skin tests with highly dilute solutions.

There are relatively few reports of illnesses associated with the raising and harvesting of castor beans. This may, in part, result from the acceptance of allergic reactions to dusts in agricultural populations, but it more likely results from the fact that the intact beans do not produce the concentrations of respirable and highly allergenic dust found in other circumstances. Canciulescu et al.(*14*) and Lupu et al.(*85*) have in recent years described hay fever, asthma, and urticaria in Rumanian farm workers engaged in threshing and bagging castor beans. Lupu et al.(*85*), although they did not give the numbers, reported 66 percent as having had hay fever; 15 percent, asthma; 2 percent, both hay fever and asthma; and 54 percent, urticaria. Panzani(*97*) stated that 3 of some 102 patients he had seen in Marseilles were employed in raising or gathering beans. Rejsek(*105*) described conjunctivitis and acute skin reactions in two employees of an oil mill whose job was to open jute sacks of castor beans; he reported that respiratory symptoms dominated the picture in those exposed to ground beans or residues after oil extraction. Small(*111*) found no evidence of difficulty in farmers raising castor beans in Southern California. Ordman(*93*) reported one case in a farmer in South Africa.

Castor oil production has led to a number of well-documented outbreaks of illness, both in employees of the mills and in residents of the vicinity. The numerous episodes involving exposures of community residents are considered in the next section of this review. Garver in 1948(*54*) reported allergic symptoms in 5 men in a processing mill, confirmed by scratch tests, intradermal tests, and passive transfer of reagins. Lucchese(*83*), the following year, described asthma in 2 employees of an oil mill in Italy and in 9 nearby residents. Dehrs, Roche, and Tolot in 1949(*43*) reported illnesses in 4 employees of an oil mill in France. These men had symptoms that suggested ricin intoxication, including malaise, headache, vomiting, diarrhea, abdominal pain, and fever. They also had respiratory symptoms: cough, dypsnea, expectoration, and edema of the face and eyelids. One individual had hematuria. In 1949 Rejsek(*105*) described his study of 28 individuals working in an oil mill in Yugoslavia; over half of these had asthma and the remainder had skin lesions. Berto and Bassi(*8*) described a number of cases of "ricinus asthma" near Padua, Italy. Most had been engaged in the pressing of castor beans at home for soap production, an exigency of World War II and its aftermath. They also studied employees of two castor oil mills in this area, but could find no positive skin reactions and no history of symptoms. Ordman(*94*) in his South African studies found that scratch tests of 131 plant employees showed 27 positive to castor bean extracts.

Panzani(*97*), who studied castor pomace problems in Marseilles, found in one series of 102 cases of castor allergy that only one case was an employee of one of the four oil mills in the area. He says that the allergies caused by castor pomace are well known to the mill owners, who eliminate possible asthmatic workers. His tests in one oil mill always proved negative. On the other hand, symptoms of acute intoxication by ricin were not uncommon. So called "ricin disease" resembles "common flu, with respiratory catarrh, mainly otolaryngitis, fever, pains, asthenia, and sometimes urticaria. This complaint, which is easily cured, only appears when the subject is exposed to thick dust."

Charpin and Zafiropoulo in 1956(*23*) described cases of asthma in the neighborhood of Marseilles oil mills. Twelve of 100 oil mill employees were described as having allergy to the pomace. Rosa et al. (*107*) found that 17 of 25 workers in Italian oil mills had some evidence of sensitivity, ranging from nasal obstruction to true asthmatic attacks; 16 had positive scratch tests. Small(*111*) reported that an oil-producing company in Southern California had an incidence of 2½ percent clinical sensitivity in its employees. Layton et al.(*76*) reported on a study of employees of another oil extraction plant in the United States. Skin tests were performed on 107 employees 10 months after the last previous castor bean run; 13 were found positive. Twelve of these 13 gave positive allergic serum transfer tests in monkeys. This compared with 58 individuals (or 53 percent) who had complained of effects from the dust the previous year. The discrepancy could indicate that some complaints were due to nonspecific irritation by dust, or were psychogenic, or that the antigens used did not represent all allergenic components in the dust. It is also possible that some of the complaints were due to toxic rather than to allergic symptoms. This has been true in similar situations.

Dust contacted or inhaled during the shipment of pomace accounts for symptoms in sailors and dock and railway workers. Bennett and Schwartz in 1934(*5*) reported allergic symptoms in a longshoreman and a sailor exposed to pomace in Brooklyn. One complained of urticaria of exposed surfaces, in addition to conjunctivitis, rhinitis, coughing, and wheezing. Skin test was positive in dilution of 1:100,000,000. Chaumont and Weil in 1956(*26*) described 6 cases of illness in dockworkers of Strasbourg; they had conjunctivitis and asthma, and their complaints of burning eyes, loss of appetite, nausea, and vomiting suggested that ricin intoxication might have contributed to the symptoms. Panzani(*97*) pointed out a similar illness experienced by dockworkers in Marseilles. Cooper et al.(*30*) described nearly 100 cases among longshoremen and railway workers in American seaports in 1959. Symptoms included nausea, headache, vomiting, and fever as well as conjunctivitis, rhinitis, and asthma, which led the authors to suspect that some of the men experienced mild ricin intoxication. The high ricin content of the pomace being handled, the extreme dustiness of many of the operations, and the absence of previous immunizing exposures reinforced this hypothesis, which unfortunately could not be tested by direct observations on the men involved.

Other groups of workers subject to potential exposures are those engaged in the blending of fertilizers. As early as 1930 Vaughn, in a discussion following a report by Barnard(*4*), commented on the occurrence of asthma in South Carolina fertilizer plants using castor pomace. Zerbst in 1944(*126*) described 40 cases of rhinitis conjunctivitis and asthma in fertilizer workers and their families.

Fertilizers containing castor pomace as a nitrogen source are a common cause of problems. Kaufman in 1950(*64*) described the characteristic events in an employee of a Kentucky landscape gardener. When the employee was exposed to fertilizer, his eyes would smart, itch, and tear; his nose would itch; he would sneeze in barrages; the skin of his face, neck, and arms would burn and itch; urticaria would appear; then he would become dyspneic and would cough and wheeze. Patch and scratch tests were positive. Berto and Bassi(*8*), in their series in Italy, described 16 cases associated with the handling of fertilizer. Ordman(*93*) described one such case in South Africa. Rosa et al.(*107*) observed similar problems in Italian farmers.

Small(*111*) called attention to the problem as seen by him in Southern California. He described 17 patients sensitive to castor bean extract by skin puncture test: 14 had asthma; 2, hay fever; 1, a chronic cough. In 11 of the 17, exposure was attributed to the use of fertilizers either by themselves or by neighbors. Small compared three sensitive patients' skin reactions produced by castor bean extracts and castor pomace that had been steam-treated; he found that the heat-treated pomace remained highly allergenic.

Ouer in 1956(*96*) reported violent asthma in a truck driver who coughed and wheezed when his neighbors used fertilizer. After an equivocal scratch test, the physician injected a 1/40,000 dilution of a castor pomace extract intradermally, with resultant vomiting, coma, profound shock, and angioneurotic edema, which required heroic therapy. This patient's intense sensitivity was confirmed subsequently by the development of status asthmaticus and unconsciousness when he entered a neighbor's home where there was an unopened bag of castor pomace in the garage. The man's clinical asthma cleared up when he moved to the Pacific Northwest where no castor-containing fertilizer was used.

Miscellaneous exposures that provide examples of extreme sensitivity include some in which the contaminating dust was in bags or other unsuspected vehicles. Bernton reported in 1945(*7*) on a well-studied case of severe asthma and urticaria in which exposure was traced to the use of sacks that presumably had been previously used for castor pomace. Figley and Rawlings(*49*) recounted allergic rhinitis, asthma, or both in workers of a coffee mill. At first the coffee was regarded as being the offending agent, but further studies by Coulson et al.(*40*) revealed that the castor bean allergen associated with the green coffee probably was a contaminant acquired when coffee was shipped in bags or in vessels previously used for castor beans or pomace. There is also the possibility, as suggested by Layton et al.(*82*), that there could be contamination with castor bean pollen or pollens and seeds of closely related plants that grow in the coffee-growing areas.

Community Illness

Because the production and use of castor pomace is limited, castor pomace allergy is an infrequent but dramatic place disease. It has been reported from many countries but only from certain locations in these countries. In most instances the cases have occurred in rather large groups (ca. 20 to 200); frequently they occur simultaneously in epidemics. Because the finely divided pomace is so dry and light, it is readily dispersed not only in the work environment but also well outside this area into the surrounding community. In such instances it becomes a community air pollutant capable of producing illnesses more than a mile from the source of emission.

The first description of such a community outbreak was published by Figley and Elrod in 1928(*48*). This report, a classic in its field, describes cases of individuals who lived or worked in the vicinity of a mill that produced several varieties of oil. Epidemics of asthma were provoked only when the processing of castor beans in the factory was coupled with suitable meteorologic conditions. The latter occurred in particular when certain winds distributed the pollutant over appropriate parts of the community. By relating attacks to wind direction, Figley and Elrod were able to develop presumptive evidence for castor pomace as an etiologic factor. Detailed studies of 8 cases, out of 30 known to the authors, were confirmatory. Cessation of the production of castor oil by court injunction stopped the attacks of asthma in the known sensitive individuals. Figley and Elrod predicted that similar situations would be found in the neighborhood of the few other castor oil mills then existing in the United States. Although studies of these other situations have never been published, brief published notes(*2*, *28*) indicate that the prediction was correct.

Miskolczy(*91*) reported on 45 cases in the vicinity of a Hungarian castor oil mill: 11 had asthma; 27 urticaria; 3, conjunctivitis without other symptoms; 2, severe bronchitis; and 2, joint swellings.

Stienen(*122*) in Germany described 18 cases of asthma near a castor oil factory; 8 percent of the population he regarded as being at risk was affected.

Mendes and Ulhoa-Cintra(*89*, *90*) reported on an outbreak of violent asthma in the community of Bauru, Sao Paulo, Brazil (a town of 60,000) that affected 150 individuals within a few days; 9 deaths were attributed to the disease. Cases were described as beginning 1 day after the introduction of hexane extraction in a nearby castor oil mill. The authors studied 30 patients carefully and found 28 were positive to scratch tests with castor pomace extracts. Local passive transfer of reagins was made with the sera of 9 patients; all provoked strongly positive reactions. Four were given provocative exposures to nebulized castor pomace thereby inducing severe bronchial asthma. Reopening of the mill after a month's inactivity led to a new outbreak, which subsided with the closing of the mill and a change of dust control.

In 1955, Ordman(*94*) reported another severe outbreak, in the Transvaal, where 197 individuals in a village of 11,000 near a castor oil plant experienced bronchial asthma. The two peaks in incidence corresponded to periods when the solvent extraction process was in operation at the factory. Cases in both white and native employees of the mill occurred prior to installation of exhaust ventilation; discharging the dust outside protected employees, but led to an outbreak of new cases in the village.

These two situations illustrate very clearly the role of the solvent extraction of the pomace in increasing the danger of illness. This is particularly true in community exposures. The very light, dry pomace produced by extraction is readily borne through the community to considerable distances as an air pollutant.

The largest community problem produced by castor-pomace air pollution so far reported is that existing in Marseilles, France, where hundreds of cases of castor allergy are found. This situation is described in a number of articles by Panzani et al.(*97, 98, 100*) and by Charpin and Zafiropoulo(*23-25*). In addition to several castor oil mills, the docks where castor products are handled in large quantities add considerably to the air pollution (Figures 4 and 5). On windy days when the "Mistral" is blowing, the allergenic dust is carried for several miles throughout the city from pomace hauled in open trucks or packed in loosely woven burlap bags. The bags enter the used-bag market and become another source of the contaminant. Some reported cases in the city are found as far as 2 to 6 kilometers from a source.

Lucchese(*83*) described a community outbreak of asthma in Figline, Italy, that was also related to the presence of an oil mill.

Community outbreaks have also been generated by the pomace escaping from fertilizer plants (Drinker(*46*), Kathren et al.(*63*)). To date, such sources seem to have produced smaller and less frequent episodes.

The community episodes so far reported do not appear to contain any clear cases of ricin poisoning. If such cases have occurred, they have not been detected with certainty, or they may have been considered to be some other type of illness, e.g., influenza. The absence of cases of ricin poisoning may also be attributed to the low dosage of exposures as compared to the dosages found in mills. It is hoped that careful observation in the future will, if opportunity offers, provide an answer to this question.

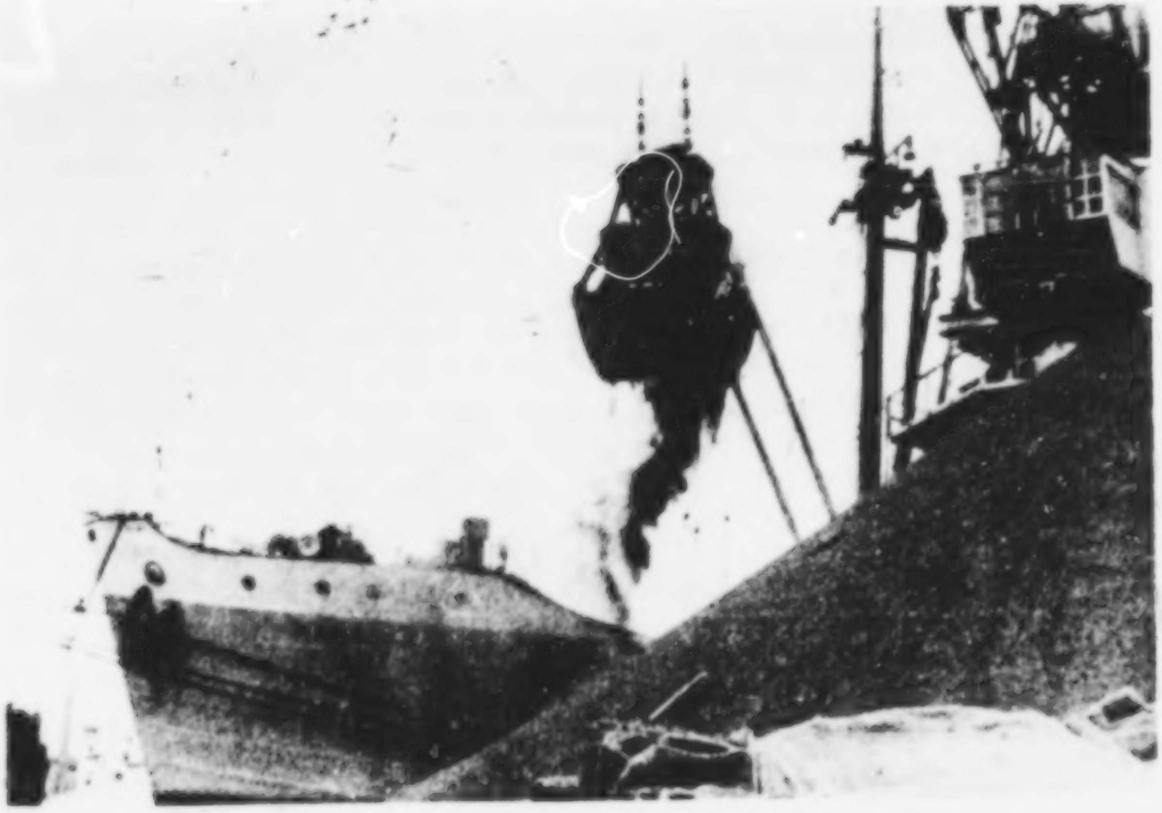

Figure 4. Crane unloading solvent-extracted castor bean pomace in Marseilles Harbour (Layton and Panzani. Intern. Arch. Allergy and Appl. Immunol. 28:116-27. 1965).

Control Measures

Because of the variety of situations in which individuals may be exposed to castor pomace, detailed advice on local control measures is impractical. Nevertheless, general principles of good industrial hygiene practice can be applied; these are particularly appropriate for use in castor oil mills and fertilizer plants and during shipping of pomace or fertliizer.

Dust concentrations should be minimized by local exhaust ventilation, the use of proper shipping containers, careful handling to reduce leakage and spillage, and good housekeeping. Sweeping should be preceded by application of an oil or sweeping compound to reduce dust. Plant effluents containing dust must not be discharged into community air under any circumstances. The most efficient dust collecting techniques possible must be employed. Also, workers should shower and change their clothing before they go home.

Pomace that has not been treated to reduce the ricin and allergen content should not be an article of commerce and should not be incorporated in fertilizers. In fact, it cannot be imported into the United States under present Coast Guard regulations(*29*). These state: "The originating bill of lading or other shipping paper shall bear the shipper's certifying statement that the pomace has been treated sufficiently to detoxify the ricin content."

Figure 5. Piles of solvent-extracted pomace on the docks at Marseilles (Layton, Panzani, et al. Intern. Arch. Allergy and Appl. Immunol. 23:225-36. 1963).

If nondetoxified pomace must be handled, in addition to the usual precautions regarding containers, spillage, and housekeeping, more stringent measures are needed because the risk of reactions is so great. Respirators, goggles, and coveralls should be worn. Respirators should be of a type approved by the Bureau of Mines for pneumoconiosis-producing dusts.

Whether detoxified or not, pomace should be shipped in sift-proof containers. Coast Guard regulations stipulate that outside containers for pomace must be sift-proof five-ply paper bags, sift-proof-paper- or plastic-lined burlap bags, or sift-proof-paper- or plastic-lined cotton bags, not over 100 pounds net weight. When castor pomace is shipped as such or is a major component of a fertilizer, the container must be properly labelled to warn those handling or using the material.

Within castor oil and fertilizer plants, there is frequently a self-selective elimination of highly sensitive individuals(*46*). The number of such individuals may be reduced by careful pre-employment review of medical histories, especially with respect to personal and family occurrence of allergy. Active asthmatics of allergic type should not work with so potent an allergen. Those with uncertain personal or family histories of allergy should be watched for development of symptoms. Hyposensitization by the usual techiques of increasing doses of allergen is not recommended because untoward reactions have been too common. Encouraging leads toward an uncomplicated hyposensitization are found in the demonstrations that other plants in the Euphorbiaceae family have cross-reacting allergens that are less hazardous but may be protective(*78, 79, 80, 99*).

The most promising current developments in control(*20, 78*) are the new techniques for detoxification and deallergenization. If tests of these prove satisfactory and if they are economically feasible, commercial castor pomace may eventually be made harmless to man and lower animals. Detailed discussions of various methods that have been tried for rendering the pomace harmless will be found in the reports of studies by Cooper et al.(*30*), Corwin et al.(*32-35*), Jenkins(*61*), and Kodras et al.(*65*) and in some of the reviews mentioned in the section on agricultural and commercial aspects. Recently, U. S. Patent No. 3294776, December 27, 1966, method of deallergenizing castor beans by treating with one molar ammonium hydroxide and with at least one part of water per part of castor bean material, has been issued to Laurence L. Layton and Frank C. Greene.

The success of carefully applied control measures is apparent in large oil mills in this country. Employee illnesses produced by castor pomace are now uncommon. They are usually detected promptly and the employee is removed from contact with the offending substance.

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the author describes his own case of asthma caused by castor pomace with which he sometimes worked in the laboratory. He had asthmatic attacks only from this substance. Symptoms began very quickly on exposure (within 5 to 15 minutes). The first symptoms resembled those of hay fever. These were followed by typical asthmatic symptoms within half an hour. This is apparently the first reported case of human allergy to castor pomace.

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(N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"*Symptoms of Poisoning in Men Exposed to Clouds of Ricin*

"During the 18 months in which this laboratory has worked with dry preparations of ricin a number of investigators have shown reactions which can definitely be attributed to exposure to ricin dust. It is evident, from our experience and from that of other laboratories, that concentrated solutions and wet or dry solid preparations may safely be handled repeatedly without poisoning via the skin. We do not wear gloves and decontaminate only with soap and water. Nevertheless we have encountered no reactions which could be attributed to contamination of cuts or skin abrasions. Such reactions as have occurred have followed accidental exposure to air borne ricin. Two types of reaction are clearly distinguished.

"*Delayed Reaction.* After a latent period of 4-8 hours there is a febrile response in which temperatures up to 103° have been recorded. Associated with the temperature there is tightness of the chest, tracheitis, dyspnea, aching joints, chills, nausea and spasmodic coughing. In 8-12 hours there is profuse sweating accompanied by disappearance of all symptoms except coughing and burning trachea. The subject feels that the temperature has broken. The actual rate of disappearance of the fever is not known but, in one case, a fall from 102.5° to 100° was recorded in 1 hour. Within 18-24 hours the patient may be entirely free from symptoms though there may be mild residual tracheitis, coughing and fever.

"*Immediate Reaction.* There is immediate sneezing. The reaction is so sharp that one may say that the susceptible subject 'smells' ricin. The sneezing is followed by a burning sensation in the trachea associated with a difficulty in breathing, with coughing and with retching. Inhalation of adrenalin spray has given transient relief but must be repeated at 5-10 minute intervals. The acute distress disappears in 1 hour or less and leaves only a mild cough, a burning trachea and, possibly, a temperature up to 101°.

"It would seem that the immediate reaction is allergic in nature. It has been seen in those members of the staff who have been most closely associated with dispersions of ricin. Some of them have previously suffered a delayed reaction. We may presume that individuals subject to the allergic reaction have been previously sensitized by an acute exposure or by chronic exposure to very low concentrations of ricin. A mild allergic reaction is elicited in susceptible individuals by much lower doses than those which will cause a delayed reaction in unsensitized individuals."

16. Cannan, R. K., and staff. **The toxicity of various preparations of W.** Office of Scientific Research and Development. Rept. OSRD No. 5525. 31 Aug. 1945. (N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"*Symptoms in Men Exposed to Airborne Ricin*

"Several cases of illness, attributable to the inhalation of ricin have occurred in personnel of the laboratory engaged in the study of the inhalation toxicity of this agent. The symptoms which have been observed are clearly distinguishable as of one of two types — immediate or delayed reactions.

"In the delayed reactions, a febrile response has followed a latent period of 4 to 8 hours. Temperatures up to 103° have been recorded. The subject has complained of tightness of the chest, tracheitis, aching joints, nausea, dyspnea and coughing. In 8 to 12 hours the onset of profuse sweating has been accompanied by alleviation of all symptoms except the cough and tracheitis which have sometimes persisted for several days.

"The immediate reaction resembles that of sensitization. The severity of the symptoms varies. In mild cases violent sneezing occurs within one minute after exposure and persists for several minutes. This reaction is so characteristic that the subject may be said to be able to smell ricin. In more severe exposures there have been asthmatic difficulties of breathing with violent coughing and retching which have disappeared within an hour leaving only a mild cough and a slight temperature.

"Subjects who responded to exposure with an immediate reaction have not shown the delayed symptoms described above. They have all worked with the agent over a long period of time. Some have suffered a delayed reaction prior to the occasion of the immediate reaction, but others have not.

"It is our impression that the delayed reaction corresponds with the toxic reaction in animals. The immediate reaction probably indicates that the subject has become sensitized to the toxin."

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24. Charpin, J., and A. Zafiropoulo. **Respiratory allergy to ricinus.** *Sem. Hop. Paris.* **32**:2843-45. 1956. French. This report is similar to the preceding report.

25. Charpin, J., and A. Zafiropoulo. **Respiratory allergy to ricinus in the Marseilles region.** *Acta Allergol.* **14**:150-60. 1959. French. This report is similar to the two previous reports. Details of occupation, age, etc. are given for cases seen by the authors in Marseilles.

26. Chaumont and Weil. **Castor pomace cakes as a pathogenic agent.** *Arch. Mal. Profess.* **17**:364-66. 1956. French. Dock workers at the port of Strasbourg have shown many bizarre illnesses that can be traced to a variety of materials handled. In the instance

here described, the symptoms were burning eyes, swollen eyelids, loss of appetite, difficulty in breathing, nausea, and, at times, vomiting. The first symptoms began after ½ hour to ½ day of work. The source of the pollutant was found to be a castor bean processing plant on the Ruhr that sent pomace to a French fertilizer plant. The castor pomace cakes were shipped in sacks to the port of Strasbourg, where they were placed on wagons. The authors give details of six cases of this occupational illness. A change of jobs where possible, good hygiene, and antihistamines were advised.

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31. Corwin, A. H., and staff. **Preparation and properties of W.** Office of Scientific Research and Development. Informal Monthly Progress Report No. 9-2-2-354. 10 Sept. 1944. (N.B. This formerly secret report has now been declassified. Because it is

not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"Hazards in Handling Ricin

"During the month, two reports on the symptoms of ricin poisoning have come to hand. One of these, from the Chicago Toxicity Laboratory, involves intoxication in humans. The other, from the Kettering Laboratory, involves only rabbits but supplements previous reports on human symptoms and points out new dangers in the handling of ricin. We wish to comment on both these reports in the light of our own experimental findings and their correlation with the literature.

"In the Chicago report (9-4-1-19, 10 Aug. 1944) two sets of reactions are mentioned, delayed reactions and immediate reactions. These sets of symptoms correlate well with two groups of symptoms described in the literature, the delayed group being classed as toxic reactions, the immediate group being classed as allergic reactions. Our comments are intended to clarify the significance of both of these reactions from the point of view of the industrial and laboratory hazards involved in the commercial production and laboratory study of ricin, and to furnish a rational basis for the treatment of the symptoms.

"The work of Spies and Coulson, published in the Journal of the American Chemical Society, has shown that the allergic symptoms mentioned above can be produced by an allergen existing in the bean. This substance is entirely nontoxic on first application. Our work, extending over a period of several months, has shown that ricin can be prepared free from this allergen by repeated recrystallization and that using a schedule which would cause sensitization either with crude ricin or with the allergen, administration of this purified toxin fails to cause sensitization or to elicit anaphylactic reactions in previously sensitized animals. From these experiments we draw the conclusion that ricin, the true toxin, is not an allergen and is incapable of either causing sensitization or of causing anaphylaxis in sensitized animals. By direct experimentation with preparations made according to the directions of Spies and Coulson we also draw the conclusion that castor bean allergen is not a toxin, causing neither intoxication nor immunity with the first injection. Quite the contrary, it causes sensitization instead of immunity and elicits toxic responses only after one or more repeated injections. While we concede that a dose schedule for desensitization may be found, this is to be differentiated from true immunization.

"As we pointed out, in the Chicago report the immediate symptoms observed on exposure to commercial ricin preparations are allergic in nature. We wish to emphasize that these allergic symptoms are not due to ricin. Consequently, we should amend the statement that 'the susceptible subject "smells ricin."' He 'smells' castor bean allergen which is an accidental impurity in ricin preparations. If a subject has never been exposed to castor bean allergen, he will not be susceptible to this and will be incapable of detecting ricin by its allergen content.

"The delayed reaction may be due to ricin itself or it may be due to a mixture of ricin symptoms with castor bean allergen symptoms. A study of the literature on human intoxication gives a fairly sharp differentiation between the groups of symptoms, but we must remember that humans have never been exposed to purified ricin under controlled conditions. The possibility of previous exposure to castor bean allergen always exists and some of the toxic symptoms may be mixed symptoms of ricin and castor bean allergen. Either group may be expected in the plant or the laboratory.

"The best differentiation between toxin and allergen symptoms recorded in the literature may be made on the basis of the mode of exposure. We may assume that the symptoms suffered by persons resident near castor oil mills are allergic in nature and do not stem from the toxin. We may assume that symptoms resulting from eating castor beans are those of the toxin in most cases, although they may be mixed with allergic symptoms due to previous exposure. Finally, we find case reports on poisoned laboratory workers whose exposure may be of either kind. In these cases, the classification of the causative agent cannot be made on the basis of the type of exposure.

"The symptoms of the unfortunate residents near castor oil mills are listed as sneezing, coughing, edema of mucous membranes, especially irritation of the eyes, congested bronchi and burning sensation in the trachea. These are to be regarded as due to castor bean allergen and not to ricin since they never result on first exposure but only after a period of residence varying from six months to over ten years.

"The symptoms of the incautious persons who ate castor beans were nausea, as early as two hours after ingestion, vomiting, diarrhea, cramps in the abdomen and extremities, suppression of urine, clouding of the sensorium. Termination may be coma, convulsions, or vascular collapse. Death may occur in forty-eight hours. These symptoms are to be regarded as those of ricin poisoning itself; with the possibility that some may be complicated, particularly as to time, by the presence of sensitivity due to previous exposure to allergen.

"The symptoms of the laboratory workers which cannot be classified from the type of exposure but can be partially classified by analogy are dull headache, swelling of joints, aching of jaws and teeth, marked intestinal pains, more or less fever, alternate diarrhea and constipation, loss of weight (certainly caused by ricin in laboratory animals), cold sweat, urticaria (probably due to allergen), nausea and vomiting.

"Unfortunately, the case histories do not include records of the temperatures of the patients, although fever is noted occasionally in the true ricin cases. We should note that our experiments show that this reaction is the opposite of that found in the laboratory mouse, whose temperature begins to drop within an hour after the administration of the toxin. On the basis of the Chicago report, fever must be considered a normal response to ricin in humans. Consideration of the case histories from Procter and Gamble shows that allergy is most common.

"Our conclusion is that the control exercised at the Procter and Gamble plant has been sufficiently rigid to prevent almost completely any exposure to ricin sufficient to bring about symptoms due to the toxin. The symptoms observed are due to the castor bean allergen. This conclusion is important in the decision as to the proper treatment to institute.

"In the Chicago report it is stated that inhalation of adrenalin spray has given transient relief in the allergic cases but that the treatment must be repeated at five to ten minute intervals. This also is in line with the observations in the literature. It has been found, however, that more lasting relief may be obtained by the use of a suspension of epinephrine in peanut oil. (Keeney, E. L., J. Allergy, Sept. 1937). The use of a gelatin epinephrine mixture has also been recommended to secure more lasting relief. A preparation such as the epinephrine in peanut oil should be available for administration in every laboratory in which the possibility of allergic reactions to ricin may occur. In view of the literature, and of the experience at the Procter and Gamble plant, this preparation should take care of the majority of cases of intoxication that are likely to occur.

"In contrast to the treatment of castor bean allergy, the findings at Edgewood, which are confirmed by Dr. Heidelberger, are that treatment of ricin intoxication by means of anti-ricin serum must be instituted within an hour in laboratory animals to be of any use. It is conceivable that later administration might decrease the severity of symptoms and is certainly to be recommended when not contra-indicated by serum sensitivity. The symptoms of ricin intoxication are so delayed, however, that the time for treatment will have expired before the usual symptoms are observed. Earlier recognition of poisoning would be very useful. Our observation that the laboratory mouse responds with a change in body temperature long before any other symptoms are observable may be of value, leading to means of recognizing intoxication earlier in cases of suspected exposure. We also wish to call attention to the possibility of treatment with an antidote which has now become a distinct probability as the result of the Canadian studies which will be referred to again below.

"The Chicago report and the Kettering Laboratory report are in disagreement as to the safety of the procedure of handling ricin so that it comes in contact with the skin. This disagreement may result in part from the different objectives of the laboratories. At Chicago, consistent and long-continued exposure to the agent on the skin is hardly to be expected. This would also be true in other laboratories where only small quantities are handled, and these infrequently. In a plant where the same operation is repeated day in and day out, the result of frequent re-exposure may be the same as that of continuous exposure. The findings of the Kettering Laboratory that the toxin itself is capable of penetrating the skin when the period of exposure is sufficiently long is of the greatest importance and certainly justifies the conclusion drawn that workers exposed under these conditions must protect even the intact skin from exposure.

"In our earlier recommendations on precautionary measures, we emphasized the importance of wearing gloves to avoid exposure of the skin. This recommendation was based upon our observation that Dr. K. A. Kraus, who worked with ricin for some years in this laboratory, had severe skin reactions on exposure to ricin. We concluded that a material was present in castor beans which was capable of penetrating the skin and that precautions against this should be observed even in the laboratory. We do not yet believe that these symptoms were due to ricin itself. We have still to find a case in which the possibility of skin penetration raised by the Cincinnati experiments has been realized in a case of human exposure. Since our recommendation was originally made, however, the work of Spies and Coulson has amply confirmed that castor bean allergen can penetrate the skin fairly readily. We note that some of the Chicago workers have acquired sensitivity to castor bean allergen by some route. The possibility that this may have been acquired by skin exposure is not excluded. For this reason we disagree with their statement that 'concentrated solutions and wet or dry solid preparations may safely be handled repeatedly without infection via the skin.' We feel that a definite element of hazard exists in such a practice and are not inclined to modify our earlier warning against it. In case of accidental exposure of ricin to the skin, we recommend immediate washing with water. The use of soap may also be of value but the use of a soap containing grit is to be avoided.

"In summary we urge avoidance of exposure to ricin preparations of any kind by any route including the intact skin. We urge immediate washing in case of exposure. In addition to immune sera, the kit for treatment of exposure to ricin preparations should include epinephrine in peanut oil for the treatment of allergic reactions, which are those most likely to be observed. To speed the institution of treatment in cases of exposure to the toxin itself, we recommend a more careful study of earlier symptoms, including temperature changes. We also recommend a careful study of possible antidotes to ricin poisoning. Finally, we recommend that all workers in the field be immunized by treatment with ricin-toxoid as soon as this is approved for human use."

32. Corwin, A. H., and staff. **Preparation and dispersion of W.** Office of Scientific Research and Development. Informal Monthly Progress Report No. W-18-035-CWS-884. 4 June 1946. (N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"Hazards in Handling Ricin

"In our Informal Monthly Progress Report No. 9-2-2-354, 10 Sep. 1944, we reviewed the cases of human poisoning with crude ricin which had been reported to that time and presented our reason for concluding that nearly all of them were due to allergic reactions. Cases of allergy to constituents of castor beans have been described for decades and it is obvious that this phenomenon constitutes one of the chief industrial hazards in the commercial processing of the beans.

"In the early work in this laboratory, a case of sensitivity to castor bean allergen occurred, and we instituted precautions designed to prevent this trouble from developing during ordinary manipulations. These precautions were sufficient to prevent serious difficulties in our laboratory until the time that we started working with micronized ricin. It is evident that a similar situation existed in Cincinnati, where Procter and Gamble Co. was engaged in the processing of ricin on a semi-commercial scale. While their problem was only that of isolation, serious difficulties were not encountered. When the problem became one of handling ball milled and later micronized ricin, difficulties increased and the earlier precautions were not found adequate too deal with the problems encountered.

"Since we have undertaken work on the dispersion of ricin for the Chemical Warfare Service, several of our personnel have become sensitized to castor bean allergen and we now regard our earlier precautions as entirely inadequate for handling of finely divided ricin which is prepared to give maximum inhalation toxicity. Material of this sort is very penetrating and readily contaminates laboratory dust. Any operation in the laboratory which stirs up the dust will be sufficient to initiate reactions in sensitized personnel. Frequent dusting with a damp cloth is helpful, but probably not adequate.

"With these difficulties in mind, we have initiated a program for studying castor bean allergen designed to bring to light adequate methods for the protection of personnel working with the substance. It must be remembered that there is no systematic study in the literature of means for the destruction of this agent so that we cannot say with certainty that any chemical or physical process, short of actual combustion, will destroy the allergen. We consider the development of adequate safety measures a necessary preliminary to further work on the dispersion of the 'live' agent and certainly an indispensable precaution preliminary to the construction of another pilot plant or factory.

"We have also pointed out on numerous occasions that the production of a toxoid against ricin is hampered by the presence of the allergen. This opinion is concurred in by Butler, Moore, and Fleming, who as a result of immunological and anaphylactic studies substantiated the conclusion that we had reached earlier that an allergen-free ricin should be prepared as a preliminary to attempts to immunize against ricin. We anticipate that our present studies may lead to methods for preparing such samples of ricin.

"*Assay Technique* — The assay of castor bean allergen is considerably more complicated than that of ricin. We wish to report at this time only preliminary data on our assay method, since we realize that many refinements will have to be introduced before we have a thoroughly satisfactory assay method. In spite of this, we have a method for assay which is roughly quantitative in that it permits estimation of the allergen with fair sensitivity to a factor of five to ten. At the moment we are more interested in increasing the sensitivity than in increasing the accuracy, since we are seeking to estimate small residual amounts of undestroyed allergen and high sensitivity should be more desirable in accomplishing this.

"The first step in setting up an assay method is to decide on the type of assay desired. In this case we might use the Dale apparatus and employ uterine strips or intestinal strips. We might, on the other hand, choose the gross anaphylactic method and employ guinea pigs, mice or other animals. We have spent some time in the exploration of these possibilities and as a result have tentatively adopted the gross anaphylactic technique, employing mice as the sensitive animals. In our studies starting about two and a half years ago and extending over a number of months, we demonstrated repeatedly that it was feasible to use mice for this work. After considerable experimentation with the method, however, we abandoned the use of mice in favor of guinea pigs because of the greater sensitivity of the latter. Since our objectives have shifted somewhat in the meantime, we have reconsidered this question and have returned to the use of mice. This is because we now desire to introduce a certain quantitative element into the assay which was not so important in our earlier work. Mice are much more homogenous biological material than guinea pigs. This makes a standard assay in terms of guinea pig units less dependable than one in terms of mouse units. We have experienced some difficulty in securing a reproducible degree of sensitization of guinea pigs to castor bean allergen. While our results with mice still leave much to be desired when compared with our ricin assay, they are much better than we can secure with guinea pigs. On the other hand, the mouse assay using the intraperitoneal route is still only about 10% as sensitive as the guinea pig assay using the intravenous route. We feel, however, that a satisfactory degree of sensitivity can be obtained with mice and for that reason are now concentrating our attention upon them.

"The choice of animal limits the choice of method. While isolated guinea pig intestines from sensitized animals respond nicely to allergen, we have not yet found means for securing this response with isolated mouse intestines. This is in accordance with the observations of earlier workers and with the fact that guinea pig intestines react to histamine while mouse intestines do not react to histamine but do react to acetyl choline.

"Finally, we must consider the fact that the use of isolated tissues is, in a sense, a less direct method than the use of whole animals. While there is every reason to suppose that identical results will be found with both methods, results secured with the isolated strip method would have to be checked with whole animals, since we are seeking protection for whole animals and not isolated strips and even this degree of extrapolation would not be justified without extensive cross-checking. For all these reasons we have tentatively chosen the anaphylactic method as preferable to the isolated strip method and have returned to the use of mice as test animals.

"Since the first of the year, when this work was resumed, we have subjected several hundred mice to anaphylactic experiments and have made progress toward the refinement of our techniques. The work is necessarily slow, however, because of the fact that the injection of the animals must take place over an interval of one to two weeks and then about three weeks more must be allowed for the development of sensitivity. Hence each experiment requires the elapse of more than a month for completion and reliable results build up slowly. Major variables which must be explored are route of administration, sensitizing dose schedule, quantity of material administered for sensitization and for shock and time elapsed after the last sensitizing dose before maximum sensitivity has been secured. In addition, factors affecting the general well-being of the colony must be explored for their influence upon the development of sensitivity and upon the phenomenon of shock. These include such matters as diet, freedom from parasites, temperature and similar variables. We have made considerable progress in the evaluation of the effects of some of these variables.

"After some experimentation, we have decided to standardize upon the use of intraperitoneal administration of both the sensitizing dose and the shocking dose. With mice we do not consider the intravenous route to be desirable because of technical difficulties. The subcutaneous route is considerably less effective both for sensitization and for shocking.

"As standard material for the work, we are using allergen prepared according to the method of Spies and Coulson, J.A.C.S., 65, 1720 (1943).

"Our dose schedule is subject to revision in the future. The experiments which we report on destruction of the allergen were based upon the assay procedure which follows. For a 20-g. mouse, CF-1 female, a dose of approximately 2 mg. of allergen dissolved in 0.2 cc. of isotonic saline was injected intraperitoneally. As a rule, the experiments were performed upon groups of four or more animals. A period of six days was allowed to elapse and a second dose was then administered by the same route. Various waiting periods to test the mice for optimum sensitivity were tried. It was found that a period of sixteen days after the second dose produced sufficient sensitivity for our present needs. This schedule is designated as a '6-16' schedule. Mice sensitized on this schedule give severe shock symptoms with doses of castor bean allergen from 2 mg. down to 10 micrograms per 20 g. mouse.

"*Action of Clorox** *on Allergen* — The Clorox used is a stabilized 5.25% solution of sodium hypochlorite.

"Experiment 1. 500 mg. of Clorox was added to 100 mg. of allergen and the mixture was stirred with a glass rod. The solution was then diluted by adding 1.0 cc. of distilled water and left twenty minutes before testing. Before injection, the solution was diluted with isotonic saline to 50 cc. Doses of 0.5 cc. containing 1 mg. of treated allergen were administered. Four mice sensitized on the 6-16 schedule were injected and showed severe symptoms of shock at the end of ten minutes. Four unsensitized mice were given the same dosage and showed no symptoms of shock.

"This experiment shows that a ratio of five to one is not sufficient to destroy allergen with Clorox. Larger amounts of Clorox could not be used without subsequent chemical treatment because of the toxic effects of the Clorox itself. For this reason the destruction of the Clorox in the presence of the allergen with heat and acid was tried. This is recorded in Experiment 2.

"Experiment 2. 250 mg. of allergen was dissolved in 25 cc. of Clorox. (This is 25 times the amount of Clorox used in the previous experiment.) The mixture was stirred for ten minutes and 25 cc. of isotonic saline was added. The solution was stirred for thirty-five minutes and 250 cc. of distilled water was added. The solution was allowed to stand under vacuum for thirty hours. It was then fanned and warmed at 55-60° for six hours, adjusted to pH 2.5 with HC1 and warmed at 60° for four hours. The solution was filtered, adjusted to pH 7 and diluted to 110 cc. with isotonic saline. It was assumed that there was a 30 mg. loss of allergen on glassware so that 0.5 cc. of solution would give a 1 mg. dose of treated allergen. Four mice sensitized by the 6-16 schedule were given 1 mg. of treated allergen and showed no symptoms of shock. Four unsensitized mice were given the same dosage and also showed no symptoms of shock.

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* Mention of commercial products does not imply endorsement by the Public Health Service.

"This drastic treatment of the allergen with Clorox shows that the material can be destroyed by oxidation. The next variant was to treat with a large excess of Clorox and to remove the excess with urea in order to prevent oxidation of the allergen during the Clorox removal process.

"Experiment 3. 500 mg. of allergen was dissolved in 50 cc. of Clorox and stirred for ten minutes. 45 cc. of isotonic saline was added and the solution stirred for 35 minutes. To remove the Clorox, 5 cc. of 10% urea solution was added and the solution stirred for 20 minutes. A 0.2 cc. dose contained 1 mg. of the treated allergen. Four 6-16 mice were injected with this dose and showed no symptoms of shock. Unsensitized controls also showed no symptoms.

"It was noted that the allergen was not wet readily by the Clorox. In another experiment the allergen was treated first with isotonic saline and then with an equal volume of Clorox in the proportions given in the preceding experiment. The saline wet the allergen much more readily. The final result was just as satisfactory. This suggests that routine washing should be carried out with water followed by Clorox. We propose to study the action of various detergents to find whether or not they will be satisfactory in increasing the susceptibility of the allergen to Clorox.

"The mice used in our last experiments with the allergen would react to 10 micrograms of allergen. This shows that a sufficient excess of Clorox allowed to stand in contact with the allergen for ten minutes will destroy at least 99.9% of the allergen.

"*Destruction of Allergen by Autoclaving* — To determine whether or not autoclaving will destroy the allergen, the following experiments were performed.

"Experiment 4. A sample of allergen solution was autoclaved at 15 pounds for twenty minutes. Three 6-16 mice were injected with a 2 mg. dose of the autoclaved solution. All three showed severe symptoms of shock at the end of ten minutes.

"Experiment 5. A sample of solid allergen was autoclaved at 15 pounds for twenty minutes. Four 6-16 mice were injected with a 2 mg. dose in 0.2 cc. of isotonic saline. All four showed severe symptoms of shock at the end of ten minutes.

"Experiment 6. A sample of allergen solution was autoclaved at 15 pounds for four hours. Four 6-16 mice were injected with a dose of 2 mg. of the solid in 0.2 cc. of isotonic saline. None of the mice showed any symptoms of shock after an hour.

"Experiment 7. A sample of solid allergen was autoclaved at 15 pounds for four hours. This sample was insoluble after autoclaving.

"The autoclaving experiments show that the usual time required for sterilization is not sufficient to destroy the allergen. Extending the time to four hours accomplishes the desired result. We propose to increase the time beyond fifteen minutes by reasonable increments to determine the minimum safe time for destruction of the material. We also propose to find a method for grinding the tough residue formed by prolonged autoclaving to a suspension fine enough to study its allergenic properties.

"In addition to the experiments cited above, we are engaged in attempts to destroy the allergen with ultra-violet light and will report our results next month."

33. Corwin, A. H., and staff. **Preparation and dispersion of W.** Office of Scientific Research and Development. Informal Monthly Progress Report No. W-18-035-CWS-884. 8 July 1946. (N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"Hazards in Handling Ricin

"Last month we noted that sufficient exposure to Clorox would destroy castor bean allergen and that sufficiently long autoclaving was also effective. It was thought that the use of germicidal lamps would provide a means for continuously purifying laboratory or factory air contaminated with the allergen. Accordingly, we have investigated the action of ultraviolet light on the allergen.

"Experiment 1. A solution of 0.2% allergen in distilled water was irradiated two and one-half hours with a G.E. H-4 high pressure mercury arc. The solution was in a quartz cell. The arc was 14 inches from the solution. The spectrophotometric trace from 220-320 millimicrons showed that no change had taken place in the solution. No decrease in physiological activity noted.

"Experiment 2. Same as 1 but 0.05% solution exposed six and one-half hours. No change noted in spectrum or activity.

"Experiment 3. The solution was 0.05%, distance 4 inches, lamp was a low pressure quartz Hg arc and exposure time was one hour. This arc has good intensity at both 25% and in the 2800's. This exposure caused a marked change in the absorption characteristics of the material. The mouse tests show that this material is more than 99% destroyed.

"Experiment 4. 0.05% solution in distilled water irradiated 15 minutes in a quartz cell with a G.E. germicidal lamp (15 watts) at a distance of 4 inches. A marked change in absorption was noted. Mouse assay shows the material still allergenic.

"Experiment 5. Same as preceding except exposure was one hour. Bio-assay shows that this material is still allergenic.

"It is evident from the preceding experiments that ultraviolet light can be used to destroy the castor bean allergen but that an ordinary germicidal lamp is not satisfactory for this application. We are investigating commercially obtainable lamps to see whether a satisfactory one can be found. It is also interesting to observe that a chemical change can be secured by ultraviolet irradiation without destruction of the allergen. Thus the only reliable test is actual bio-assay. Since the germicidal lamp is very strong at 2536 and this is a point of minimum absorption, and since the low pressure arc had considerable intensity in the 2800's and this corresponds with the absorption maximum of the tyrosine in the molecule, we suspect that the allergenic property can be destroyed by destroying the tyrosine by irradiation in the 2800's. We shall follow this line in our first experiments on the selection of new lamps."

34. Corwin, A. H., and staff. **Preparation and dispersion of W.** Office of Scientific Research and Development. Informal Monthly Progress Report No. W-18-035-CWS-884. 9 Aug. 1946. (N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

"*Hazards in Handling Ricin*

"We have continued our studies on the hazards of handling ricin and of possible chemical and physical methods for overcoming them. Further information on the stability and destruction of the allergen is given in the succeeding sections.

"*Ultraviolet Treatment* — Two of the amino acids which absorb in the region of the allergen absorption are tyrosine and tryptophane. We are recording herewith absorption studies on tyrosine, histidine, and tryptophane with the G.E. germicidal lamp. Irradiation increases the opacity of the solution even though the tyrosine does not absorb strongly at the point of maximum intensity of the lamp. The change noted is similar to that found with the allergen whose activity had not been destroyed by the irradiation.

"There is a small increase in the opacity of the histidine even though this does not absorb strongly where the lamp is intense. In the before and after comparison of tryptophane also an increase in opacity is found even though the amount of tryptophane absorption at 2536 is smaller than at 2800.

"The foregoing results show that some chemical action can be induced in tyrosine, histidine and tryptophane by irradiation at 2536 even though none of these materials have an absorption maximum at this wavelength. We hope to add information in the near future concerning the effects obtained by irradiation at 2800.

"*Chemical Treatment of Allergen. Autoclaving.* In a series of four experiments, a 1% solution of allergen and the solid material were treated for one hour and for one-half hour in the autoclave at 15 pounds pressure. We conclude that half an hour at 15 pounds is sufficient to render the allergen solution incapable of producing shock but that this time of exposure leaves some residual activity in the solid. Therefore, one hour's exposure should be used to destroy the solid.

"*Formaldehyde* — Because of its use in toxoid preparations, it is of importance to learn whether or not formaldehyde is capable of destroying the shocking activity of castor bean allergen. Two experiments were performed. In the first of these a 1% solution of allergen in isotonic saline was treated with formalin. 0.05 cc. of 37% formaline was used per 5 cc. of allergen solution. After standing for 1½ hours at 28° the solution was tested. No decrease in activity was noted.

"In the second experiment the conditions of exposure were identical with those used in best toxoid preparations. 60 cc. of a 0.66% solution of repurified allergen was mixed with 60 cc. of a 0.25 M Na_2CO_3 — $NaHCO_3$ buffer solution at pH 9.0. 0.60 cc. of USP formalin (35%) was added. Three-quarters of the mixture was incubated at 45° for 79 hours. At the end of four hours after mixing, the nonincubated fraction was tested with sensitized mice. The preparation showed less activity than untreated allergen.

"The incubated fraction was then tested on mice. It may be estimated from the results that approximately 75% of the activity has been destroyed by this treatment. Since identical treatment of the toxin destroys well over 99% of the toxicity, we again conclude that the allergen is more difficult to deactivate than the toxin. We may note that our estimates were that about 80% of the antigenic power of the toxin is destroyed by this treatment.

"A sample of ricin toxoid, prepared from crystalline ricin, 5x, was tested for allergenic power on mice sensitized with the allergen. This sample showed definite residual allergenic power.

"We may conclude that formaldehyde is not satisfactory as a laboratory reagent for the destruction of allergen nor does the treatment used in the preparation of toxoid suffice to destroy allergenic activity.

"*3% Hydrogen Peroxide* — Two experiments were performed. 100 mg. of allergen was treated with 10 cc. of 3% H_2O_2 at pH 7 and at pH 3. Our conclusion from these experiments is that 3% H_2O_2 does not destroy allergen, whereas it readily destroys toxicity in the toxin."

35. Corwin, A. H., and staff. **Preparation and dispersion of W.** Office of Scientific Research and Development. Informal Monthly Progress Report No. W-18-035-CWS-884. 9 Sep. 1946. (N.B. This formerly secret report has now been declassified. Because it is not readily available, the pertinent portion is quoted in full except for minor alterations; e.g., substitutions of words for code letters.)

    "*Destruction of the Allergen*

    "We have continued our search for a satisfactory lamp for the destruction of castor bean allergen by ultraviolet irradiation. Using the data in the publication by Forsythe, Adams, and Barnes (Denison University Bulletin, Journal of the Scientific Laboratories, Vol. 37, p. 127), we are able to correlate the energies at the critical wavelengths, believed to be 2700 to 2900, with the amount of destruction of the allergen.

    "As reported last month, the G.E. germicidal lamp causes little or no destruction of the allergen. The output of this lamp in the region of 2800 to 3165, which encompasses most of the range we believe to be active, is 0.033 watts. This month we have tried a type S-4 sunlamp. Its output from 2800 to 3165 is 2.48 watts, a factor of 75. This proves to be sufficient to destroy about half of the allergen at a distance of four inches in 80 minutes. We do not consider this at all satisfactory. The quartz Uviarc, with an output of 17.9 watts in the same range, a factor of 540 over the germicidal lamp, completely destroys the allergen, as reported in July. Unfortunately, this is not a practical lamp for the irradiation of a large working space."

36. Corwin, A. H. **Toxic materials in the castor bean.** *Chemurgic Dig.* June 1954. pp. 14-16. A careful and detailed description of the nature and action of the toxin and allergen of the castor bean is given. The development of antitoxic immunity and allergic sensitivity with repeated exposure, the dangers inherent in castor bean production and handling, and safe manufacturing procedures are discussed.

37. Corwin, A. H. **Toxic constituents of the castor bean.** *J. Med. Pharm. Chem.* 4:483-96. 1961. The author discusses work on ricin and castor bean allergen done by himself and his staff over several years. Other related work, chemical properties and

composition of both substances, the intimate relationship between the two substances, and methods of partial and complete separation are considered. Considerable information is given on agglutinating properties and on toxoid production.

38. Coulson, E. J., J. R. Spies, E. F. Jansen, and H. Stevens. **The immunochemistry of allergens. VIII. Precipitin formation and passive transfer reactions with allergenic proteins from cotton seed and castor beans.** *J. Immunol.* **52:259-66. 1946.** The allergenic proteic-polysaccharidic fractions from cotton seeds and castor beans are precipitogenic when administered to rabbits. Ovalbumin is more uniformly effective than either in stimulating preciptin formation. The passive transfer technique provides a more sensitive method for detecting cotton seed and castor bean antibodies in sera than the precipitin method.

39. Coulson, E. J., J. R. Spies, and H. Stevens. **The immunochemistry of allergens. VI. Anaphylactogenic properties of a proteic component of kapok seed, and the relationship of kapok seed antigens to cotton seed antigens.** *J. Immunol.* **49:99-116. 1944.** There are allergenic constituents in cotton seeds, castor beans, and kapok seeds. The kapok tree is botanically related to the cotton plant, and its allergens are similar or identical. Since immunological cross reactions between the proteins of related species are frequently found, it is possible to use serological studies to trace phylogenetic relationships in plants and animals. Quite unrelated species, however, may also have identical or similar antigenic components.

40. Coulson, E. J., J. R. Spies, and H. Stevens. **Identification of castor bean allergen in green coffee.** *J. Allergy.* **21:554-58. 1950.** Figley and Rawling's discovery of castor bean allergen contamination of green coffee beans was confirmed and found to be common. Identification of the castor bean allergen was done by means of Moody's modification of the Schultz-Dale technique. Nonspecific muscle irritants were first eliminated. Quantitative comparisons of extracts taken from coffee beans with the pure castor bean extracts showed that contamination of the coffee was present to the extent of 1 to 5 ppm. The contamination was shown to be on the surface of the coffee beans. Powdered roasted coffee showed no trace of the allergen. Apparently roasting inactivates the allergen.

41. Coulson, E. J., J. R. Spies, and H. Stevens. **The allergen content of castor beans and castor pomace.** *J. Am. Oil Chem. Soc.* 37:657-661. 1960. A precipitin method for quantitating the allergenic content of castor bean is described. The allergenic content of 10 different varieties of decorticated, defatted beans ranged from 6.1 to 9.0 percent. Several samples of commercial pomace contained much less allergen. The authors suggest that current milling processes are capable of reducing the allergen to a degree that is significant in the production of castor pomace allergy.

42. Coulson, E. J., J. R. Spies, H. Stevens, and J. H. Shimp. **The immunochemistry of allergens. X. Anaphylactogenic properties of allergenic fractions from castor beans.** *J. Allergy.* **21**:34-44. 1950. This paper reports a study of the sensitizing, anaphylactogenic, and other properties of the CB-1A protein-polysaccharide and the CB-65A subfraction of this compound, which is free of carbohydrate. These are natural preformed proteins isolated from the castor bean. The carbohydrate portion of CB-1A played no part in its antigenic specificity but enhanced its sensitizing capacity over that of CB-65A. The presence of an unidentified dialyzable antigen was also detected.

43. Dehrs, V., L. Roche, and F. Tolot. **Allergic accidents from ricinus in industry.** *Arch. Maladies Profess.* **10**:26-32. 1949. French. This article presents four cases of respiratory allergy due to castor bean in workers at a castor oil mill. The cases noted general malaise, headache, vomiting, diarrhea, abdominal pain, and respiratory symptoms such as cough, dyspnea, expectoration, and a feeling of constriction in the chest. They also had edema of the face and eyelids, conjunctivitis, and fever. One case had hematuria. Symptoms disappeared rapidly when the workers left the mill.

44. de Laet, M. **Work injury due to ricin.** *Arch. belges med. sociale et hyg.* **4**:453-55. 1946. French. A case report is given with discussion of legal aspects. The patient developed a very severe dermatitis very rapidly when he handled cakes of castor pomace. His reaction was much greater than that of fellow workers, who had only a mild traumatic dermatitis from handling the rough material. It is uncertain whether or not this was an allergic reaction. The author decided it was not.

45. Djuricic, I., V. Danilovic, B. Bozovic, D. Karajovic, and M. Savicevic. **Prevention in occupational allergy.** *Fol. Allerg.* **6**:207-31. 1959. French. In this detailed revue of occupational allergies, particularly as found in Yugoslavia, the material on castor bean sensitivity is found on pages 216 and 217. Paragraphs 2 to 4 are somewhat confusing because of an apparent typographical error in which the castor plant (le ricin) is not always clearly distinguished from the toxin ricin (la ricine). This review contains material from a study previously carried out and reported to the Serbian Academy of Sciences by these same authors. Of 200 inhabitants in a village that produced castor beans, 12 were allergic to the beans. In 9 cases, asthma was the principal symptom. Half of these 200 people were skin tested with a large group of allergens; 22 were found to be sensitive to castor bean extract.

46. Drinker, P. **The practice of industrial hygiene.** *Am. Ind. H. Assoc. Quart.* **11**:101-09. 1950. On page 107 the author describes an incident with which he was concerned in which air polluted by castor pomace produced disease. The case was not

brought to trial because the defendant company discontinued the operation involving the castor pomace. The source of the pomace was a fertilizer factory in a crowded industrial area. Cases of asthma occurred in about 10 percent of the employees in a foundry across the street whenever the wind blew in their direction. There were no cases in the fertilizer plant because sensitive workers left to seek other jobs. This type of industrial emission should be relatively easy to control. This same situation is also described on page 73 of Industrial Dust, 2nd ed., Drinker, P., and T. Hatch, McGraw-Hill, Inc., New York, 1954.

47. Ehrlich, P. **Experimental investigation of immunity. I. On ricin.** *Deut. Med. Wchnschr.* **17**:976-79. 1891. German. Early experiments in antitoxic immunology were hampered by the difficulty of obtaining pure bacterial toxins in quantity. Some experiments were carried out with more readily available toxalbumins. Ehrlich reports his use of ricin for this purpose and the results of his initial experiments in the production of artificial immunity in mice.

48. Figley, K. D., and R. H. Elrod. **Endemic asthma due to castor bean dust.** *J. Am. Med. Assoc.* **90**:79-82. 1928. This is apparently the first description of a community situation in which asthma and other allergies were produced in the neighborhood around a castor oil factory. The illnesses were caused by air pollution with castor pomace. The influence of wind direction in determining the precise sector of the city that would be bothered on any particular day is described. Eight cases are described in detail. Thirty cases were known to the authors, and there were probably at least 55 others. All cases experienced relief from symptoms on leaving the vicinity of the plant and recurrence on returning. The factory was closed by court injunction, which terminated the episode.

49. Figley, K. D., and F. F. A. Rawlings. **An industrial hazard as a contaminant of green coffee dust and used burlap bags.** *J. Allergy.* **21**:545-53. 1950. Nine cases of allergy to castor bean dust are reported. These occurred in employees of a coffee plant who were exposed to green coffee and the bags in which it was shipped. No cases were found in individuals exposed to roasted coffee. The castor bean dust contaminates the coffee in several ways: (1) by reuse of bags that had previously contained castor beans for shipping coffee, (2) by reuse of bags previously used for shipping castor pomace, and (3) by contamination of sacked coffee in transit in vehicles or ships where castor bean dust or pomace is present.

50. Flexner, S. **The histological changes produced by ricin and abrin intoxications.** *J. Exper. Med.* **2**:197-216. 1897. This study deals with the fundamental pathology of ricin poisoning. Pathological changes due to ricin were peritoneal hemorrhage, ascites, lymphadenopathy, and swollen Peyer's patches. No mucosal ulceration

was seen. The whole picture resembles that of the "typhoid intestine." The mucosa of the stomach was congested. Splenomegaly with splenic pulp swelling was always present. Focal hepatic necrosis, subcutaneous tissue edema, renal glomerular and tubular changes, fatty degeneration of the heart, and necrosis and hemorrhage of the adrenals were invariably present.

51. Follweiler, F. L., and D. E. Haley. **Toxicity of the castor bean.** *J. Amer. Med. Assoc.* **84**:1418. 1925. Three cases characterized by rhinitis, asthma, intestinal symptoms and/or polyarthritis due to contact with castor beans are discussed. All of the cases occurred in laboratory workers. Symptoms ceased when contact with the beans was discontinued. No attempt is made to distinguish toxin and allergen, but the symptoms are recognized to be of an allergic nature.

52. Freedman, S. O., R. Shulman, J. Krupey, and A. H. Sehon. **Antigenic properties of chlorogenic acid.** *J. Allergy.* **35**:97-107. 1964. This paper deals with the problem of artificial induction of antibodies with chlorogenic acid in animals and the subsequent demonstration of such antibodies by means of various tests. Most of the work was done with chlorogenic acid, green coffee extracts, and caffeic and quinic acids. Material from castor beans was employed in the hemagglutination reactions where it produced a partial inhibition. Various samples of chlorogenic acid displayed considerable differences in antigenicity. The possible reasons for this are discussed.

53. Freedman, S. O., A. I. Siddiqi, J. H. Krupey, and A. H. Sehon. **Identification of a simple chemical compound (chlorogenic acid) as an allergen in plant materials causing human atopic disease.** *Am. J. Med. Sci.* **244**:548-55. 1962. Workers in the coffee industry who developed allergic symptoms on exposure to factory dusts gave positive reactions to water extracts of green coffee only. Fractionation by chromatography showed skin sensitivity to be primarily associated with a fraction containing numerous phenolic compounds. Tests with known phenolic compounds found in green coffee showed reactions only to choloregenic acid. Neutralization tests indicated this to be the active component in the whole coffee extracts. This acid is present in castor bean and orange and is shown to be related to the whole reaginic extract by neutralization tests.

54. Garver, W. P. **Castor bean sensitivity.** *J. Lab. Clin. Med.* **33**: 1613. 1948. A very brief report is given of five cases of castor bean allergy. The symptoms are not given. The patients were skin tested and found sensitive to castor pomace extract. Thirteen controls were also tested; two had positive reactions.

55 Grabar, P., and A. Koutseff. **Differentiation of the toxin ricin and an allergen in the castor bean.** *Compt. Rend. Soc. Biol.* **117**: 700-01. 1934. French. Castor beans and castor pomace both

contain ricin and an allergen. Ricin is more thermolabile than the allergen. Ricin is precipitated by ammonium sulfate, whereas the allergen is not. Ricin is not dialyzable, but the allergen is.

56. Grabar, P., and A. Koutseff. **On the preparation of ricinus allergen and its separation from ricin.** *Compt. Rend. Soc. Biol.* **117**:702-04. 1934. French. Two methods are described. One resembles that of Osborne, Mendel, and Harris for the preparation of ricin. In this method both toxin and allergen are extracted with their biologic properties intact. The other method employs boiling, which destroys the ricin but does not damage the allergen.

57. Grimm, V. **Which climatic factors are significant for the asthmatic?** *Veroffentl. a.d. Geb. Med. Verwalt.* **26**:553-834. 1928. German. This article is frequently referred to as an early, or as the first, description of a community air pollution asthma outbreak due to castor pomace. It is not. This long article contains among other data an abridged version of the Toledo, Ohio, episode described by Figley and Elrod.

58. Hansen, K. **Allergy to ricinus dust.** *Heft. Unfall.* **44**:221-27. 1953. German. The problem of whether occupational allergies should be classified under German law as work accidents or as occupational diseases is discussed. Allergy to castor beans is used as an example because its great potency makes it a more striking problem. The discussion is not conclusive, at least in respect to the German legal criteria.

59. Hansen, K. **Allergy.** 3rd ed. Geo. Thieme Verlag. Stuttgart. 1957. German. This is sometimes given as a primary reference. It is not. There is, however, a good review of castor pomace allergy on page 209.

60. Jacoby, M. **Ricin, Abrin, Crotin.** In: *Handbuch der Experimentellen Pharmakologie.* A. Heffter, ed. Vol. 2, pt. 2. pp. 1735-47. Springer Verlag, Berlin. 1924. German. The pertinent material is in a paragraph on page 1744. Jacoby states that he had a laboratory assistant who developed asthmatic attacks when minute amounts of castor pomace reached his nasal mucosa. This man had previously worked in Ehrlich's laboratory when the early experiments on ricin were being done and had been sensitive to castor products for many years.

61. Jenkins, F. P. **Allergenic and toxic components of castor bean meal: review of the literature and studies of the inactivation of these components.** *J. Sci. Food and Agr.* **14**:773-80. 1963. Evidence is presented indicating that treatment of castor bean meal for 1 hour with steam at 15 psi destroys ricin and inactivates the allergen. If this treatment does not produce nutritional damage to the meal, the method would be useful for converting the meal into a safe and inexpensive food supplement for farm animals.

62. Jones, D. B. **Proteins of the castor bean — their preparation, properties and utilization.** *J. Am. Oil Chem. Soc.* **24**:247-51. 1947. The author reviews the composition of castor seeds and of the cake or pomace remaining after removal of the oil from the bean. The various proteins present in the pomace are then discussed. Considerable attention is given to ricin and the allergen present. Current and potential uses of the pomace are reviewed. An extensive reference list is included.

63. Kathren, R. L., H. Price, and J. C. Rogers. **Airborne castor bean pomace allergy, a new solution to an old problem.** *Arch. Ind. Hyg.* **19**:487-89. 1959. Four cases of asthma, rhinitis, conjunctivitis, and urticaria are described as occurring in workers in a pipe company. They were affected when the wind blew from the direction of a fertilizer plant about 250 yards distant. Castor pomace used in this plant apparently produced the allergic symptoms. When the fertilizer factory changed from the use of the very dry pomace resulting from pressing and solvent extraction to the oily pomace produced by pressure extraction alone, the allergic symptoms in the four pipe factory workers ceased.

64. Kaufman, M. **Allergy to castor bean dust with report of a case.** *Ann. Allergy.* **8**:690-94. 1950. A case in a Negro employee of a landscape gardening firm is described. It was produced by castor pomace contained in the fertilizer. The patient was also sensitive to house dust. His removal from contact with the fertilizer produced slow improvement.

65. Kodras, E., C. K. Whitehair, and R. MacVicar. **Studies on the detoxification of castor seed pomace.** *J. Am. Oil Chem. Soc.* **26**:641-44. 1949. Castor pomace is highly toxic to animals. Of the various methods of detoxification tried, the most satisfactory proved to be autoclaving for 15 minutes at 125°C. This destroyed the toxin without altering the physical characteristics of the pomace. Feeding experiments with detoxified pomace showed a low biologic value. Analysis of protein amino acids showed relatively high amounts of glutamic acid and a serious deficiency of tryptophan and methionine. Lysine was marginal.

66. Kraus, K. A. **Studies on Ricin.** Ph.D. thesis. The Johns Hopkins University, Baltimore. 1941. The pertinent material is in Appendix I. The author reports on the development in himself of allergy to castor bean dust. At first the symptoms were principally of the hay fever type; as time went on, asthmatic symptoms became predominant. Control of symptoms was established by working with castor products in a well-ventilated hood.

67. Layton, L. L., B. T. Dante, L. K. Moss, N. H. Dye, and F. DeEds. **Electrophoretic fractionation of soluble antigenic proteins from the seed of *Ricinus communis* (castor bean).** *J. Am. Oil Chem. Soc.* 38:405-10. 1961. A water-soluble, heat-stable protein com-

ponent of castor seed meal was subjected to paper-strip electrophoresis in buffers of different chemical composition, pH values, and ionic strengths. Phosphate buffer at pH 7.4 to 8.0 and in ionic strength of approximately 0.05 gave a sharp resolution of castor seed proteins into bands that would bind bromophenol blue. Spies' allergen CB-1A was resolved into six or more components at pH 8.0. Each band was found to be antigenic in sensitized guinea pigs by means of passive cutaneous anaphylaxis. Five bands were positive in sensitive humans.

68. Layton, L. L., and F. C. Greene. **Passive transfer of human allergies to prosimians: skin reactions in the lemuroid *Nycticebus* coucang (slow loris).** *Proc. Soc. Exp. Biol. Med.* **115**:667-71. 1964. Previous experiments showed the possibility of passive cutaneous transfer of castor bean and other allergic sensitivities from man to monkeys. The present study shows that the process is possible in a lemuroid. This finding presents some interesting possibilities for the study of primate taxonomy.

69. Layton, L. L., and F. C. Greene. **Systemic allergic shock induced in monkeys passively sensitized by intravenous injection of human allergy serum.** *Intern. Arch. Allergy and Appl. Immunol.* **25**:193-99. 1964. Previous experiments in passive transfer of allergic sensitivity by means of human serum in anthropoid skin indicated the possibility of a systemic passive transfer. This was attempted by means of intravenous injections into *Macaca irus* monkeys of human sera from individuals sensitive to castor bean. This systemic passive transfer was shown to be successful by the demonstration of positive scratch tests to the appropriate allergen and by the development of typical allergic shock reactions on intravenous injection of the allergen. Monkeys may prove useful in the study of allergic shock and its treatment.

70. Layton, L. L., F. C. Greene, J. W. Corse, and R. Panzani. **Pure chlorogenic acid not allergenic in atopy to green coffee: a specific protein probably is involved.** *Nature.* **203**:188-89. 1964. This letter describes recently performed work that contradicts Freedman, et al. on the role of chlorogenic acid in allergy to coffee, castor beans, etc. An earlier study by Layton, Panzani, et al. had indicated some area of disagreement with Freedman, et al. In this study, several preparations of chlorogenic acid prepared by different methods were tested by means of passive cutaneous anaphylaxis in monkeys. Sera from 29 French patients sensitive to castor bean dust and 12 Canadian patients sensitive to green coffee were employed. The mostly highly purified chlorogenic acid produced no sign of allergic activity, but the cruder forms caused some degree of activity. Coffee extracts also produced positive reactions.

71. Layton, L. L., F. C. Greene, F. DeEds, and T. W. Green. **Electrophoretic fractionation of a carbohydrate-free allergenic prep-**

aration from the seed of *Ricinus communis* (castor bean). *Am. J. Hyg.* **75**:282-86. 1962. Allergenic fractions CB-65A and CB-1A and a water soluble protein fraction CB-S.R.I. of the castor bean were compared by electrophoretic analysis. The carbohydrate-free CB-65A fraction resolved into five bands. The other two fractions produced seven bands. Apparently the removal of carbohydrates from CB-65A also removes some protein. All five bands of CB-65A produced skin reactions in sensitive individuals.

72. Layton, L. L., F. C. Greene, R. Panzani, and J. W. Corse. **Allergy to green coffee.** *J. Allergy.* **36**:84-91. 1965. Clinical skin tests on patients and passive transfer tests in monkeys indicate that allergy to green coffee bean dust does not involve chlorogenic acid. Allergy to green coffee is apparently a typical atopic sensitivity to specific plant protein. Previous indications that chlorogenic acid was the allergen involved appear to have been due to the presence of protein allergen as an impurity in the chlorogenic acid used. The green coffee allergy cases showed no cross reactions to castor bean, roasted coffee, orange, or other fruits.

73. Layton, L. L., W. E. Greer, F. C. Greene, and E. Yamanaka. **Passive transfer of human atopic allergies to Catarrhine and Platyrrhine primates of suborder Anthropoidea.** *Intern. Arch. Allergy and Appl. Immunol.* **23**:176-87. 1963. Passive transfer allergy tests were carried out in a number of anthropoid species with sera from human individuals sensitive to castor bean, ragweed, and other allergens. Most of the species tested proved satisfactory for use in this type of testing.

74. Layton, L. L., S. Lee, and F. DeEds. **Diagnosis of human allergy utilizing passive skin sensitization in the monkey *Macaca irus*.** *Proc. Soc. Exp. Biol. Med.* **108**:623-26. 1961. The technique of passive cutaneous anaphylaxis utilizing the monkey, *Macaca irus*, is described. Sera of patients suspected of being sensitive to the allergens of castor pomace were tested with satisfactory results.

75. Layton, L. L., S. Lee, and F. DeEds. **Passive cutaneous anaphylaxis in the detection of seed antigen of *Ricinus communis* (castor bean).** *J. Am. Oil Chem. Soc.* **38**:597-600. 1961. Tests of the allergenic properties of alkaline hydrolyzed castor pomace by means of passive cutaneous anaphylaxis in guinea pigs are reported. Hydrolysis at pH 12.4 for 32 minutes apparently destroyed antigenicity, but treatment for 20 minutes did not.

76. Layton, L. L., S. Lee, E. Yamanaka, F. C. Greene, and T. W. Green. **Allergy skin tests upon castor-bean-sensitive humans and passively sensitized cynomolgus monkeys.** *Intern. Arch. Allergy and Appl. Immunol.* **20**:257-61. 1962. Skin tests with the CB-1A fraction of castor beans were carried out on the 107 employees of a factory that processed castor beans period-

ically. Twelve percent of the employees were found to be positive. This correlated well with the percentage reporting definite severe allergic symptoms. The mild and vague symptoms reported were thought to be due to dust irritation. Passive transfer tests in monkeys had a high correlation with the direct skin tests.

77. Layton, L. L., L. K. Moss, and F. DeEds. **The complex nature of castor sensitivity.** *J. Am. Oil Chem. Soc.* **38**:76-80. 1961. Although the great majority of clinical allergic reactions to castor plants and their products are related to the allergen that Spies and Coulson designated CB-1A, there is some evidence that this is not the only allergen present in the plants. Pomace, pollen, and female blossoms were tested, and incomplete cross-reactions indicated that other allergens are present in the plant, particularly in the pollen and blossoms.

78. Layton, L. L., R. Panzani, F. C. Greene, T. W. Green, and J. D. Smith. **Castor bean allergy as cross-reactive hypersensitivity to the spurges (Euphorbiacelae): absence of reaction to chlorogenic acid in primary allergy to castor beans.** *Intern. Arch. Allergy and Appl. Immunol.* **23**:225-38. 1963. Tests for antigenic relationships between castor pomace, bull nettle, green coffee, and chlorogenic acid were carried out on 4 American and 33 French individuals known to be sensitive to castor beans. Both passive cutaneous anaphylaxis and direct scratch tests were employed. Relationship between sensitivity to castor beans and bull nettle seeds was established. No reactions to chlorogenic acid or green coffee were detected in individuals sensitive to beans.

79. Layton, L. L., R. Panzani, E. Yamanaka, and F. C. Greene. **Neutralization of specific reagins in monkeys passively sensitized by cross-reactive allergy sera.** *Proc. Soc. Exp. Biol. Med.* **112**:945-50. 1963. Blood sera from 60 allergy patients in Marseilles, France, were examined by the reagin passive transfer test in macaque monkeys. Twenty-six of the sera were highly reactive with castor bean protein. Six of these reactive sera were also highly reactive with castor pollen extract. By means of the phenomenon of reagin neutralization with castor pollen extract, sites passively sensitized with these six sera were rendered nonreactive to the pollen allergens; the pollen-desensitized sites were still highly reactive to the seed protein.

80. Layton, L. L., E. Yamanaka, and F. C. Greene. **Use of monkeys to demonstrate allergic cross-reactions among the Euphorbiaceae *Ricinus communis, Poinsettea pulcheorima* and *Euphorbia esula*.** *J. Allergy.* **33**:276-80. 1962. Cross-reactions were previously demonstrated between castor pomace, castor flowers, and castor pollen. These apparently share some common antigens. In this study cross-reactions are also demonstrated between the castor plant and two of its close relatives from the same family. Implications for human allergy are discussed.

81. Layton, L. L., E. Yamanaka, F. C. Greene, and F. Perlman. **Atopic reagins to penicillin, pollens and seeds: thermolability, titer and persistence in the skin of passively sensitized macaque monkeys.** *Intern. Arch. Allergy and Appl. Immunol.* **23**:87-94. 1963. Tests were made on human sera that were reaginic to penicillin, grass pollens, or castor beans for (a) thermal stability at 56°C, (b) dilution titer, and (c) persistence of specific reactivity in monkey skin after passive transfer. Human allergy serum antibodies that passively sensitize monkeys are inactivated at 56°C. Some sera may be diluted 32-fold and still sensitize monkeys. Skin-sensitizing antibodies persist in monkeys for at least 2 weeks after transfer. In all these respects the serum antibodies that sensitize monkey skin by the passive transfer technique resemble those that sensitize human skin in the same manner.

82. Layton, L. L., E. Yamanaka, S. Lee, and T. W. Green. **Multiple allergies to the pollen and seed antigens of *Ricinus communis* (castor bean).** *J. Allergy.* **33**:232-35. 1962. The authors had previously shown that seven or more protein components of castor seeds are antigenic. In this study ten individuals shown by PCA skin tests in monkeys to be allergic to castor bean were skin tested for sensitivity to castor pollen. Nine gave a mild reaction to the pollen. Sera from these ten individuals and sera from three other individuals who were also allergic to castor beans were tested by PCA in *Macaca irus.* Six of the nine with positive skin sensitivity to pollen also gave positive PCA reactions in the monkey, as did two of the three not previously skin tested. Apparently castor pollen and castor pomace share common antigens. Reactions to the pollen are milder than to the pomace. The pollen could sensitize to the pomace.

83. Lucchese, G. **Bronchial asthma and allergy to castor bean dust.** *Settimana medica.* **37**:165-70. 1949. Italian. The author describes an outbreak of asthma due to castor pomace in Figline, Italy. Cases were associated with the operations of an oil mill that periodically processed castor beans. There were 2 cases among the 25 mill workers. Others were found in people working or living in the vicinity of the mill. Eleven cases are described in detail. Specific desensitization was successful in a number of cases. (A complete translation of this report is included in a later section of this bibliography.)

84. Lupu, N. G., G. T. Dinischiotu, R. Paun, I. G. Popescu, L. Fotescu, M. Zamfirescu-Gheorghiv, C. Olaru, C. G. Iota, B. Moscovici, C. Molner, N. Ursea, J. Lowe, S. Weiner, A. Avachian, I. Bicelesan, and I. Dumitrescu. **Studies on allergy to the castor oil plant.** *Stud. Cercet. Med. Intern.* **2**:639-52. 1961. Rumanian. The authors' study of the occurrence of allergy among the inhabitants of two districts in Rumania where castor beans are grown for oil production is reported in part. Numerous cases of specific allergy to castor plants were found. The symptoms, mainly

respiratory, developed in most cases after several years of intermittent contact with the plant. Threshing of the bean pods was the most important agricultural procedure in the production of allergic symptoms. Extraction of oil from the beans was not done in these communities.

85. Lupu, N. G., G. T. Dinischiotu, I. G. Popescu, R. Paun, L. Fotescu, M. Zamfirescu-Gheorghiv, C. Olaru, C. G. Iota, B. Moscovici, C. Molner, and N. Ursea. **Investigations on castor oil plant allergy in a rural collectivity.** *Acta Allergol.* **17**:268-75. 1962. This is an abridgment in Englsh of the previous paper.

86. Lupu, N. G., G. T. Dinischiotu, I. Paun, I. G. Popescu, L. Fotescu, M. Zamfirescu-Gheorghiv, C. G. Olaru, B. Moscovici, C. Molner, and N. Ursea. **Occupational asthma of ricinus growers.** *Concours Med.* **84**:5843-46. 1962. French. This article is similar to those previously published on this topic in Rumanian and in English.

87. Matsui, K., H. Sakamoto, T. Kojima, and A. Inada. **A symptom-complex due to inhalation of castor bean dusts which occurred among workers in an oil mill.** *Jap. J. Ind. Health.* **4**:669-77. 1962. Japanese. Workers exposed to castor pomace for a short period had severe conjunctivitis, rhinorrhea, chills, and fever. Those who were exposed for longer periods developed dyspnea and cough. The first group of symptoms, which followed initial exposure to the pomace, was accompanied by leucocytosis, albumimuria, and excessive excretion of urobilinogen. This picture could be reproduced in rats, and was considered to be due to ricin poisoning. The second group of symptoms (dyspnea and cough) was allergic in nature, occurred after months of exposure, was accompanied by eosinophilia, and was attributed to the allergen contained in the pomace.

88. McIntyre, W. E. **The castor bean, industrial oilseed.** *Sci. Monthly.* **75**:42-46. 1952. The many and increasing industrial uses of castor oil are discussed. Although in earlier years beans were not grown commercially in the United States, now a significant part of our oil production is from domestic beans.

89. Mendes, E. and A. B. Ulhoa-Cintra. **Etiology of epidemic asthma in Bauru.** *Rev. Paul. Med.* **43**:29-44. 1953. Portuguese. This is a detailed study of an outbreak of asthma and other allergic symptoms in persons residing in the vicinity of a castor oil plant in Bauru, S. P., Brazil, and in visitors to the town. Thirty of the 150 cases reported are described in detail. There were nine deaths. The cases all gave positive reactions to skin testing with castor pomace extract. In four cases, symptoms were reproduced by artificial exposure to castor pomace. (A complete translation of this report is included in a later section of this bibliography.)

90. Mendes, E., and A. B. Ulhoa-Cintra. **Collective asthma, simulating an epidemic, provoked by castor bean dust.** *J. Allergy.* **25**:

253-59. 1954. This article describes the same situation as the previous reference. It is not, however, a translation of the previous paper. In this report there is less clinical detail, but more general information. The responsible castor oil mill had been operating in the community for many years. The acute siutation arose when an improved extraction process that produced a drier pomace was installed. Closing the plant terminated the outbreak. Reopening produced further cases, which ceased on closing the plant again. The plant is now successfully operated with efficient dust collection equipment.

91. Miskolczy, V. **Mass allergy connected with the manufacture of castor oil.** *Nepeges.* **31**:253-56. 1950. Hungarian. The author describes an outbreak of allergic illness in Hungary that occurred in the vicinity of an oil factory. A few of the cases were those occupationally exposed, but the majority were people living in the vicinity of the plant. Symptoms occurred only when the factory was processing castor beans. There is an excellent description of the manufacturing process in relation to the production of allergenic dusts. The author discusses 45 cases that came under his care; but over 100 cases were known to have occurred. Of the cases presented, 11 suffered from asthma; 27, from urticaria; 3, from conjunctivitis; 2, from bronchitis; and 2, from joint swelling. All patients maintained the same symptoms during repeated attacks. Successful treatment with antistin is described. It is interesting that the author apparently considers these allergic reactions to be due to a sensitivity to ricin, rather than to a separate allergen in the castor pomace. (A complete translation of this report is included in a later section of this bibliography.)

92. Moule, Y. **On the physicochemical properties and the mechanism of action of ricin.** *Arch. Sci. Physiol.* **5**:227-43. 1951. French. The author succeeded in preparing a highly purified ricin. This had a toxicity similar to that of the highly purified substances prepared by other authors. Electrophoretic analysis demonstrated the presence of two components in the ricin. These were present in approximately equal amounts. Ultracentrifugation showed that they had the same molecular weight. They are equally toxic, and the toxic property is inseparable from the proteolytic property of these substances. Toxicity is therefore thought to be due to proteolytic action on essential cellular substances.

93. Ordman, D. **Allergic sensitivity to the castor bean *(Ricinus communis)*. South African cases of vasomotor rhinitis and bronchial asthma caused by the inhalation of castor bean dust.** *So. African Med. J.* **24**:141-44. 1950. A report of six cases of allergic symptoms due to castor beans. The illnesses were of the hay fever or asthma type. With one exception of uncertain origin, the exposures were occupational. They occurred in an employee in a fertilizer factory, a salesman, a chemist, a farmer, and a botany teacher.

94. Ordman, D. **An outbreak of bronchial asthma in South Africa affecting more than 200 persons caused by castor bean dust from an oil processing factory.** *Intern. Arch. Allergy and Appl. Immunol.* **7**:10-24. 1955. The author describes the rapid growth of the castor bean processing industry in South Africa. He gives a detailed description of two community outbreaks of asthma caused by air pollution with castor pomace. The role of winds and their direction is described. An investigation of an oil factory is also presented.

95. Osborne, T. B., L. B. Mendell, and I. F. Harris. **A study of the proteins of the castor bean, with special reference to the isolation of ricin.** *Am. J. Physiol.* **14**:259-86. 1905. The authors give a short summary of prior work on isolation of the toxin ricin. In very extensive laboratory work that was done to isolate the various protein fractions of the castor bean, 12 series of extractions were performed, and all the various fractions were tested on animals. The authors were concerned only with the isolation of directly toxic substances, not with sensitizing agents. Results showed that castor beans contain proteins similar to those of other oil seeds, i.e., crystallizable globulin, coagulable albumin, and proteoses. Their elementary chemical composition and reactions were determined. The toxalbumin was isolated in pure state by an improved method without impairing its solubility of physiological action. The effect of ricin on various species of animals was determined. The effect of digestive enzymes on the toxin was also studied. Evidence for the protein nature of ricin is discussed.

96. Ouer, R. A. **Allergy to castor bean meal; case of anaphylactic shock and gastrointestinal hemorrhages.** *Ann. Allergy.* **14**:367-69. 1956. Castor pomace sensitivity was suspected in the patient. A scratch test with castor bean extract was negative. An intradermal test with a 1/40,000 dilution produced a very violent, nearly fatal reaction.

97. Panzani, R. **Respiratory castor bean dust allergy in the south of France with special reference to Marseilles.** *Intern. Arch. Allergy and Appl. Immunol.* **11**:224-36. 1957. This is an excellent report of 102 cases of asthma, rhinitis, or urticaria caused by castor pomace. All of the cases had positive skin tests. The author reports 14 cases of experimental reproduction of asthma by means of exposure to the pomace. He notes that the majority of his patients were allergic to other substances. He feels that hyposensitization is dangerous and uncertain because it is difficult to obtain allergen that does not contain some ricin.

98. Panzani, R. **Clinical forms of respiratory allergy from castor bean dust.** *Presse Med.* **66**:1788-91. 1958. French. This report is essentially similar to the preceding article.

99. Panzani, R. **Study of the allergic crossreaction between castor bean and spondylocladium.** *Intern. Arch. Allergy and Appl.*

Immunol. **21**:288-93. 1962. French. Because it is difficult if not impossible to prepare ricin-free extracts of castor bean allergen, desensitization with such extracts is not practical. Possibly a nontoxic extract of some other plant that demonstrates cross-immunity consistently with castor plants could be employed for desensitization. In a systematic search for such a cross-relation, numerous molds were tried. All castor-sensitive patients reacted to spondylocladium sp. extracts but less extensively than to castor extracts. Allergic patients not sensitive to castor plants were rarely sensitive to this fungus. A study of desensitization to castor pomace with spondylocladium extracts is underway and will be reported later.

100. Panzani, R. and L. L. Layton. **Allergy to the dust of *Ricinus Communis* (castor bean): clinical studies upon human beings and passively sensitized monkeys.** *Intern. Arch. Allergy and Appl. Immunol.* **22**:350-68. 1963. This report deals with various observations and experiments on the 478 cases of castor pomace allergy that have been studied by Dr. Panzani in the Marseilles area of France. Opportunities in this area for exposure and clinical studies including symptoms, scratch tests, Prausnitz-Küstner tests, and experimental exposures are described. There is considerable discussion of the relationship between sensitivity to castor pomace and other substances, particularly a spondylocladium mold, and to the pollen of the castor plant. The latter cross-reaction is specifically explored in California by Dr. Layton by means of passive transfer tests with monkeys. The article concludes with a brief section on prevention and treatment.

101. Popescu, I. G., R. Paun, C. Molner, M. Zamfirescu-Gheorghiv, and N. Ursea. **Preliminary data concerning specific desensitization treatment in ricinus asthma appearing in ricinus growers.** *Stud. Cercet. Med. Intern.* **3**:499-503. 1962. Rumanian. The desensitizing material was prepared by the Grabar method. A four-fold dilution was employed in desensitization attempts in 60 sensitive people. Two to six 45-day treatment periods were alternated with 60-day rest periods. Results were encouraging, but full evaluation must be made after a longer interval — at least 2 years.

102 Ratner, B., and H. Gruehl. **Respiratory anaphylaxis in guinea pigs due to castor bean dust.** *Proc. Soc. Exper. Biol.* **25**:661-62. 1927-28. This is a preliminary report on the work later reported in full in the Am. J. Hyg. in 1929. (See Reference 103.)

103. Ratner, B., and H. Gruehl. **Respiratory anaphylaxis (asthma) and ricin poisoning induced with castor bean dust.** *Am. J. Hyg.* **10**:236-44. 1929. Guinea pigs were exposed in specially made inhalation chambers. The effects of toxin and allergen were studied by varying the amount of ricin in the pomace used. Large amounts of ricin caused the animals to die of ricin poisoning; small amounts produced immunity to the toxin. Sensitivity to the allergen developed on repeated exposure. Re-exposure

after an interval produced death by anaphylaxis in previously sensitized animals. This type of reaction in guinea pigs is thought to be closely related to asthma in man.

104. Ratner, B. **Dust hypersensitiveness with special reference to castor bean.** *J. Allergy.* **2**:1-5. 1930. This is a review of the previous work of Ratner and Gruehl.

105. Rejsek, K. **Allergic manifestations during processing of castor beans.** *Casop. Lek. Cesk.* **88**:609-13. 1949. Czech. The author investigated a group of 32 cases caused by castor beans and pomace in employees of an oil mill. Four others were known to have occurred. Over half of the 32 had asthma, and the remainder suffered from skin lesions. More than half of the plant employees were ill. Successful treatment with antihistamines is reported. Also, hygenic improvements in the plant were helpful in prevention. (A complete translation of this report is included in a later section of this bibliography.)

106. Robbins, W. J. **A case of supersensitiveness to the poisonous action of the castor bean.** *Science.* **58**:305-6. 1923. A case of asthma and rhinitis in a botany student is briefly reported. The illness was relieved by discontinuing contact with the castor beans.

107. Rosa, L., G. Bergami, G. Cenacchi, and G. Zaccardi. **Allergy to ricinus.** *Bull. Sci. Med. (Bologna).* **131**:307-17. 1959. Italian. This article describes cases seen at the authors' clinic, and also investigations of workers in a nearby castor oil factory. Ten cases found in the course of their practice are discussed. Seven of these were farmers exposed to fertilizer containing castor pomace. Of the 25 workmen in the factory, 17 showed some evidence of sensitivity, although many were of mild degree. Sensitization tended to be more severe with increasing duration of employment. (A complete translation of this report is included in a later section of this bibliography.)

108. Rosa, L., G. C. Cenacchi, and G. Bergami. **Allergy to ricinus. Note 1. Clinical contribution.** *Fol. Allerg.* **5**:451-64. 1958. Italian. Nine cases of allergy due to castor bean dust are described. The severity of the illness is emphasized. Only one of the patients gave a family or personal history of previous allergy. This indicates the great antigenic potency of this allergen, which is capable of producing illness in those not previously affected by other allergens.

109. Schern, K. **Experimental studies of the practical utility of anaphylaxis.** *Arch. Tierheilk.* **36**:suppl. 590-610. 1910. German. The subject of this report is the development of sensitive methods for the detection of dangerous contaminants in animal feeds. Sensitivity to castor beans was induced in guinea pigs so that they could be used for detection of this contaminant through their anaphylactic reaction when exposed to feeds containing

this substance. Similar experiments were carried out with other substances. This appears to be the first published recognition of the allergenic potential of the castor plant. Further studies along these lines were carried out, e.g., Ueber die Verwendung der Anaphylaxie zum Nachweiss von Verfälschungen der Futtermittel. Berlin. Tierartzl. Wehr. **27**:113-15. 1911.

110. Siddiqi, A. I., and S. O. Freedman. **Identification of chlorogenic acid in castor bean and oranges.** *Canad. J. Biochem. Physiol.* **41**:947-52. 1963. Chlorogenic acid was identified in castor pomace and in orange pulp extracts by paper chromatography, by infrared and ultraviolet spectrophotometry, and by immunological cross-neutralization. In the latter test, the neutralization was not complete. The significance of the results by the same laboratory in relation to other studies on chlorogenic acid is discussed.

111. Small, W. S. **Increasing castor bean allergy in southern California due to fertilizer.** *J. Allergy.* **23**:406-15. 1952. A report is given of 17 cases of asthma and/or rhinitis caused by sensitivity to castor pomace. Most of the cases were exposed to fertilizers containing the pomace. The increasing production and uses of castor oil are discussed. The author suggests that fertilizers containing the pomace be labeled to indicate its presence.

112. Small, W. S. **Wider dissemination of castor bean allergen, factors presaging increasing incidence of disease in California.** *Calif. Med.* **78**:117. 1953. The great increase in California in the production and the importation of castor beans and in the manufacture of castor oil and pomace is discussed. The latter is extensively used in fertilizer. The potential dangers in the increased production and use of this potent allergen are pointed out.

113. Snell, M. A. **Castor bean pomace exposure**. *Arch. Ind. Hyg.* **6**:113-15. 1952. A review article.

114. Snell, W. H. **Hypersensitivity to the castor bean.** *Science.* **59**: 300. 1924. This letter reports the author's own allergy to castor beans. The symptoms were rhinitis and wheezing, which were relieved by discontinued contact and provoked by renewed contact with castor beans or dust therefrom.

115. Spies, J. R., and H. S. Bernton. **Response of nonallergic persons to injected castor bean allergen CB-1A.** *J. Allergy.* **33**:73-83. 1962. Eighty-two percent of 132 nonallergic persons showed no response to a series of injections of castor bean allergen. Four of the recipients developed slight clinical reactions. Twelve developed blocking antibodies after more than one series of injections. Clinical symptoms and blocking antibodies did not appear in the same individuals.

116. Spies, J. R., and E. J. Coulson. **The chemistry of allergens. VIII. Isolation and properties of an active proteic-polysaccharidic**

fraction, CB-1A, from castor beans. *J. Am. Chem. Soc.* **65**:1720-25. 1943. A nontoxic allergenic protein polysaccaride fraction, CB-1A, was isolated from castor beans. The procedure used was that developed for isolation of an allergenic fraction, CS-1A, from cotton seeds. Defatted castor bean meal contained 1.8 percent of CB-1A. CB-1A differed from CS-1A in that it contained no tryptophan. Minimal shocking and sensitizing doses for guinea pigs were determined. Positive cutaneous tests were obtained on sensitized persons with dilutions of $1:10^6$.

117. Spies, J. R., E. J. Coulson, H. S. Bernton, H. Stevens, and A. A. Strauss. **The chemistry of allergens. XIV. Effect of heat and pH of the precipitin reaction and reagin neutralizing capacity of the castor bean allergen CB-1C.** *Ann. Allergy.* **18**:393-400. 1960. Testing methods are described in detail. The CB-1C fraction proved to be more heat resistant in acid solutions. The degree of heat resistance found was unique among known allergens.

118. Spies, J. R., E. J. Coulson, H. S. Bernton, P. A. Wells, and H. Stevens. **The chemistry of allergens. Inactivation of the castor bean allergens and ricin by heating with aqueous calcium hydroxide.** *Agr. and Food Chem.* **10**:140-45. 1962. Effects of heating castor bean meal with aqueous calcium hydroxide at various times and temperatures are described. Toxicity was measured in guinea pigs. Allergenicity was measured by immune rabbit antiserum, skin test in a susceptible individual, and passive transfer reactions in humans with reactive human serum. The remarkable stability of the castor bean allergen is discussed.

119. Spies, J. R., E. J. Coulson, D. C. Chambers, H. S. Bernton, and H. Stevens. **The chemistry of allergens. IX. Isolation and properties of an active carbohydrate free protein from castor beans.** *J. Am. Chem. Soc.* **66**:748-53. 1944. A carbohydrate-free protein fraction, CB-65A, was isolated from fraction CB-1A from castor beans. The process of separation resembled that employed for the isolation of the analogous fraction, CS-60C, from cotton seeds. The allergenic properties of CB-1A seem to be mainly inherent in the new fraction, CB-65A.

120. Spies, J. R., E. J. Coulson, D. C. Chambers, H. S. Bernton, H. Stevens, and J. H. Shimp. **The chemistry of allergens. XI. Properties and composition of natural proteoses isolated from oilseeds and nuts by the CS-1A procedure.** *J. Am. Chem. Soc.* 73:3995-4001. 1951. Many nuts and seeds contain allergens that are "natural proteoses" and can be isolated by the same procedure. Detailed comparison of the allergens from a number of sources is made, showing their differences and similarities.

121. Spies, J. R., E. J. Coulson, and H. Stevens. **The chemistry of allergens. X. Comparison of chemical and immunological properties of CB-1A preparations from domestic castor beans and**

Brazilian castor bean pomace. *J. Am. Chem. Soc.* **66**:1798-99. 1944. The allergenic fractions of Brazilian and domestic castor beans appeared to be identical by all the test methods employed.

122. Stienen, H. **Asthma from castor pomace.** *Arch. Gewerbpath and Gewerbhy.* **11**:143-49. 1942. German. The author briefly describes an episode that resulted in a law suit. The suit was brought by 18 people who lived in the vicinity of a castor oil factory and constituted 8 percent of the people in the factory district. All had asthma due to castor pomace air pollution from the oil factory. The main part of the article is devoted to a detailed description and discussion of a case of asthma in a millhand who was exposed to castor pomace in the process of cleaning used sacks that were contaminated with the pomace.

123. Woringer, P. **Ricinus allergy.** *Zeit. Klin. Med.* **143**:499-509. 1943-44. German. This report is similar to the 1935 paper. (Reference 125.)

124. Woringer, P **Ricinus allergy.** *Sem. Hop. Paris.* **21**:661-64. 1948. French. Three cases of castor pomace allergy that occurred in a physician and two laboratory workers who had contact with pomace are presented in detail.

125. Woringer, P., P. Grabar, and A. Koutseff. **Physiopathologic study of castor bean allergy.** *Compt. Rend. Soc. Biol.* **118**:60-62. 1935. French. Three cases of castor pomace allergy that occurred in laboratory workers who handled this material are presented.

126. Zerbst, G. H. **Unusual hazard in a fertilizer factory.** *Ind. Med.* **13**:552. 1944. This is a short report of an outbreak of allergic illness in a South Carolina fertilizer plant that used castor pomace. There was considerable absenteeism due to asthma. No ventilation or other precautions against dust were employed in the factory. The workers were found to have poor personal hygiene. They also normally wore their work clothes home, which produced additional asthma cases in some households. Correction of these defects greatly reduced the number and severity of reactions.

127. Zimmerman, L. H. **Castor beans, a new oil crop for mechanized production.** pp. 257-88. In: **Advances in Agronomy,** Vol. 10. Academic Press, New York. 1958. A comprehensive and detailed discussion is presented of the agricultural aspects of castor bean production. In 1957 the plant was grown commercially in nine states in the United States.

SELECTED TRANSLATIONS

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RICINUS ASTHMA

By R. Berto and D. Bassi

In Italy, one of the least known allergies of the respiratory system is that attributable to ricinus. In reviewing the vast bibliography on the subject of allergic diseases, we found that the cases described were, almost exclusively, by foreign authors.

The first epidemic caused by the inhalation of castor seed powder was reported by Hansen; Grimm recorded a second, comprising 30 persons, six with constitutional allergic symptoms, which occurred in the vicinity of a castor oil manufacturing plant. In 1929 Ratner and Gruehl demonstrated experimentally the possibility that an allergy from ricinus powder can provoke typical asthmatic attacks in guinea pigs sensitized by this powder. In 1935, Buton observed a case of rhinitis in a woman chemist that occurred whenever her laboratory was engaged in the elaboration of castor seeds; the rhinitis invariably disappeared 2 or 3 hours after she left the laboratory.

Anaphylactic phenomena caused by ricinus were observed in themselves by Borchardt and Alilaire. In Jacoby's laboratory, an attendant who 20 years previously had continuously assisted Ehrlich in his experiments with ricin exhibited asthmatic symptoms every time the smallest ricinus particles reached his nasal mucosa.

Reports on asthma attributable to castor seed powder were made by Bernton in 1923; by Figley and Elrod in 1928 among workers in Ohio engaged in the manufacture of ricinus products (the population lived in the vicinity of the plant, and students attended a school in the area); and at various times since then by Blank, Coulson et al., Spies, Zerbst, Stienen, Buton, Bennett and Schwartz, and Ratner.

Recently, Lucchese described 11 cases of asthma attributed to castor seed powder among workers of a factory engaged in the extraction of residual oil from the husks, and among the population of the surrounding areas.

We intend to take up in extenso the argument already treated in an advance note communicated to the 48th Congress of the Italian Society of Internal Medicine (Societa Italiana di Medicina Interna).

Ricinus communis is a member of the Euphorbiaceae family; it is a herbaceous or shrub-like plant from tropical Africa, growing wild in Calabria, Sicily, and Sardinia, and widely cultivated in other regions of Italy. In the temperate and cold zones the plant is an annual, but the varieties that grow spontaneously in Asia and on Mediterranean shores are perennials. In Sicily and Sardinia it has the appearance of a veritable tree and may attain a height of 5 to 6 meters. On the basis of certain particular characterictics of the seeds and leaves, several varieties are distinguished: megalospermus, purpureus, lividus, and inermis.

In 1934 in the Rieti experimental granicultural station, studies were initiated by the late Senator Strampelli for the creation of a new variety of ricinus from two types: the Veronese red (rosso veronese) and the small common type (comune piccolo). Subsequently, in 1937, the type "M6 Strampelli," which united the characteristics of productivity and early maturation, was introduced.

Castor seeds are oval, 15 to 20 mm long and 5 to 12 mm wide, convex on the dorsal side, and flattened on the ventral. A raphe extends from the caruncle at the apex to the chalaza at the other extremity. The seeds are marbled, polished, shiny, and greyish-yellow or reddish-brown. Their shell is crusty and fragile, with a white membrane (endopleura). The seeds are enclosed in a three-celled septicidal capsule with numerous spikes on the outside; these capsules open spontaneously at maturity and fling out the seeds. The capsules are gathered when they are completely dry, but prior to their spontaneous bursting. In addition to mineral salts, pectic substances, a small amount of cholesterol, bitter and resinous substances, a lipase, and between 40 and 50 percent oil, the seeds contain ricin toxalbumin, which resembles somewhat the microbial toxins and which is destroyed by heat at 100° C and is sensitive to light. It seems that the content of the toxic component is represented in the proteinic substance. The lethal dose in a rabbit is between 3 and 5 mg per kg body weight. The ricine, on the other hand, is a nontoxic alkaloid whose formula corresponds to the methyl ester of ricinic acid.

For years individuals sporadically affected by ricinus asthma had been coming for observation and treatment to our Medical Division, but the frequency of this type became so particularly striking shortly after the start of the recent war, that Prof. Scimone advised a study of the situation and issued directives.

We report briefly some observations that may indicate the direction of the research.

Case 1: C. Ferdinando, age 54, of Pieve di Soligo, agricultural storekeeper. Family anamnesis does not indicate any recurrent diseases or allergic manifestations. One brother died of gastric ulcer; another of perforated appendicitis. He has three healthy sons. He eats a great deal and drinks about a liter of wine per day; until July of last year he had smoked a packet of tobacco and five to six cigarettes per day. Bowel movements and diuresis were normal.

At 16 he suffered from bronchitis, which ran its course in a few days. He remained well until September of last year when he went to Agordino to acquire some timber. His activities were extremely fatiguing for about 10 days; perhaps as a result of these exertions, he felt a little unwell for a couple of evenings and had cold chills, which however did not keep him from his normal tasks. Back with his family, he started out one evening to clean the slope of the hill and cover it with a mixture of pig-fat and ground-castor-seed fertilizer; he was seized with a dyspneal crisis with severe coughing so intense that he was forced to give up this work and return to bed.

The attack of dyspnea and cough continued during the night and the following day. The physician who had been called carried out the usual antiasthmatic therapy and advised him to remove from the room a quilt made from the silk of silkworms and also a tanned rabbit skin. Nevertheless, the symptomatology persisted. He was taken to the local hospital where he recovered his customary good health. But, when he returned to his home, where he kept the jar of pig fat and seeds in the room, the crises recurred toward the end of the first night and continued to recur so that after a stay of 5 days in the house he was forced to go outside to sleep, about a hundred meters away, still in the vicinity, but where no ricinus was being cultivated. No asthmatic attacks resulted when he stayed in the laboratories of a tobacco factory in the vicinity. Additional tests for other allergenic factors were negative.

Physical examination of the respiratory apparatus revealed: thorax symmetrical, scarcely expansible; vocal fremitus, preserved in the entire ambit; plessic sound, tendency toward hypersonority; expiration, prolonged; some sibili, more numerous in the left hemithorax. Other data were: ear, nose, and throat examination, negative; Wassermann and equivalent tests on the blood, negative. Leucocytic formula: neutrophils, 70; lymphocytes, 26; eosinophils, 2; monocytes, 2.

The cutaneous reactions carried out according to Walcher with pollens, powders, foods, hairs, feathers, etc. gave the following results: ricinus cake++++, ricinus husk ++++, ricinus leaves+++, and bark of ricinus wood++++. All the other tests were negative, including ricinus pollen.

Case 2: B. Pietro, age 41, of Portogruaro, farmer, married. There were no recurrent diseases or asthmatic conditions in his ancestry. He completed the usual military service. He has six healthy sons. He is moderate in the use of alcohol, eats with moderation, and smokes a pipe. Bowel movements and diuresis were normal. He lives in a malarial zone and at 28 contracted tertiary malaria whose typical attacks of short duration disappeared as a consequence of quinine treatment lasting some 20 days. At 33, he was operated on for a radiologically verified duodenal ulcer from which he had suffered for 4 years; after the surgery he had no further complaints, even when not adhering to the prescribed diet.

The current morbid picture developed 3 years ago in January, while he was taking part for the first time in the grinding of castor seeds usually done by the women in the kitchen; he experienced intense dyspnea and an irritating dry cough, which lasted for about 10 minutes and terminated with the emission of a small amount of viscid sputum. During the next 10 days, he had similar dyspneal attacks, particularly at night, accompanied by coughing; these attacks were very much less intense than the first one. At the end of each, he emitted a small quantity of viscid sputum. For 5 or 6 years prior to his first attack, the patient had cultivated ricinus in his own fields with no reactions, and during the entire month immediately preceding the onset of the first attack, he had engaged in the removal of seeds from the capsules at night without feeling the least disturbance. The seeds are ground preparatory to the manufacture of soap for laundry purposes (not for personal hygiene).

The next year, in August, while taking part in the decapsulation of the dried castor seeds, which this time was carried out with sticks and not manually as in the previous year (the operation with sticks easily produces the breakage of many seeds), he began to experience stenoses of the nasal passages followed by rhinorrhea and a dry insistent cough lasting for about 20 minutes and ending with the emission of a small amount of viscid sputum. During the next 6 days the attacks manifested greater intensity than the first one, then were less frequent and milder, and disappared after another 6 days. During the first 3 days, however, the patient continued to take part, though not constantly, in the threshing of seeds. Afterwards he was well until this year.

Twelve days ago while observing the grinding of castor seeds in the kitchen, he had an unexpected asthmatic attack, more intense than the previous ones; the attack recurred also the next day, and he was forced to consult a health worker, who prescribed the usual symptomatic therapy and advised him to enter a hospital.

All the objective tests related to the thorax, which appeared ample, statically and dynamically symmetrical, with a slight decrease in vocal fremitus; plessic sound of a hypersonorous character; weak murmur, conspicuous diffusion of hisses and sibili.

Radiological examination showed a hyperdiaphanous state of the two respiratory fields; accentuation of the hilar area bilaterally; clear apices; free diaphragms; normal heart and aorta.

The leucocytic formula furnished the following picture: neutrophils, 62; eosinophils, 10; lymphocytes, 24; monocytes, 4. Sputum examination was negative for Koch bacillus; the Wassermann reaction, negative; and the ear, nose, and throat examination, negative.

Cutaneous reactions carried out according to Walcher with pollens, powders, foods, hairs, feathers, etc. gave the following results: ricinus seeds^{++++}, ricinus cake^{++++}, ricinus leaves^{+}, nondialyzed ricin^{++}, and dialyzed ricin^{+++}; all other tests were negative, including ricinus pollen and oil.

Case 3: B. Pietro, age 41, of Biancade di Roncade, chicken vendor, married. He has a brother suffering from gastric ulcer. Patient had been rejected for military service on account of thoracic perimeter deficiency. He was married at 23 and has five healthy children. He is a heavy wine drinker and eater and had smoked two packets of tobacco per day until 8 months ago. He was constipated, but diuresis was normal. In childhood he suffered from bronchitis and later, from pneumonia. Until age 15, he suffered frequent bronchial attacks during the spring and autumn.

Since then, he was well for 26 years until the spring of last year. While making soap from castor seeds, he suddenly suffered a typical asthmatic attack lasting a half hour and ending with the emission of a small quantity of viscid whitish sputum. The health worker advised him to remove from the house all objects that might represent the possible cause of the attack, including the castor seeds. Two months afterward on entering the house where castor seeds were being ground, he suffered another attack, lasting for a half hour. When he left the house, the attack ended. A few days later the patient fell ill with bronchial pneumonia of which he was cured in 8 days. After about 10 days he again experienced malaise and dyspnea but not in the form of an attack.

The thorax exhibited static and dynamic symmetry. Vocal fremitus was weak; plessic sound, clear; expiration, prolonged; diffuse sibili and hisses; ear, nose, and throat examination, negative; sputum examination, negative for Koch's bacillus; Wassermann reaction, negative. Leucocytic formula: neutrophils, 25; neutrophilic metamyelocytes, 1; eosinophils, 24; basophils, 1; lymphocytes, 47; monocytes, 2.

The cutaneous tests performed according to Walcher with pollens, powders, foods, hairs, and feathers, gave the following results: Rumex pulcher++++, Antoxanthum odoratum++, Alopecurus agrestis++++, Calendula officinalis++, Arthemisia vulgaris++, Aster ericoides++++, Phleum bulbosum++, Parietaria officinalis++, Tenacetum vulgare ++++, Planera japonica++, ricinus seeds+++, ricinus leaves++, cake+, dry ricin and in solution++++. Cutaneous reactions was negative for ricinus pollen and oil.

At the same time these cases came under our observation, there was increased interest in identifying the allergenic substance in the ricinus seeds. Attention was first directed to ricin because, on account of its classification as a toxalbumin, it offered the requisites for being an antigen.

Ricin is contained in a considerable quantity in the shell of the seed. The brown shell is crusty and fragile because the sclerotic cells are longer than wide, and it has very thick walls (Mascherpa). In the various manipulations to which the seed is subjected in soap production, it is this layer that is liberated with the greatest ease to come into contact with the nasal and bronchial mucosa.

Not finding ricin commercially available, we had to prepare it for use in the cutaneous reactions.

In addition we proposed to carry out the passive transfer test for sensitivity according to Prausnitz-Kustner and to produce the attacks artificially.

For the extraction of ricin, Kobert recommends the following method: The pulverized seeds are treated with ether and then with alcohol to remove the fats, lecithin, cholesterol, alkaloids, etc. Finally, the seeds are ground with a 10-percent NaCl solution at 37° C to 40° C for 24 hours, and the filtrate from the grinding is precipitated by the addition of ammonium sulfate to saturation; the precipitate is dried at room temperature and may be preserved for years. NaCl and ammonium sulfate may be eliminated by dialysis.

Later Kobert described a second procedure: Precipitation of the concentrated seed extracts with an equal volume of alcohol and filtration without heating on a well-dried and slightly warmed glass filter. The ricin obtained in this manner has a lower ash content but becomes more easily insoluble. Using the first method, we subjected a portion of the ricin obtained to dialysis and used the other portion, undialyzed, for the cutaneous reactions.

In animal experiments, ricin provokes a local irritation at the site of application after a prolonged period of latency, and then an intense inflammation. When the ricin is injected under the skin, the subcutaneous cellular tissue becomes gelatinous, and the lymph nodes swell and redden.

Whether ricin is introduced intravenously or subcutaneously, the lethal dose is always the same, and a period of latency is always necessary. When the application is oral, however, the lethal dose should be 100 times greater than when the toxin is administered by other routes because of a partial destruction of the poison by the gastric juice and incomplete absorption.

The changes the toxin undergoes in vivo are not too well known; it is known, however, that after introduction it is no longer demonstrable as such in the organism. In vitro it has been shown that ricin exerts an agglutinating action on the red blood cells of various animal species (in order of decreasing sensitivity: pigeon, guinea pig, rabbit, dog, horse, ox). It is not known whether an entirely similar action takes place in vivo or whether the mechanism of death in case of intoxication should be attributed to this very same action.

Although the leucocytes and even cells of fixed tissues (conjunctiva, intestinal mucosa) may be agglutinated by ricin, agglutinations have not been observed in the blood of animals that have been poisoned by ricin. We noted, however, the changes described by Muller: decrease in the number of erythrocytes and in globular resistance; retarded coagulation; and hyperleucocytoses.

Twelve hours after introduction of the most minute dose of toxin, the animal exhibited a drop in body weight. After 24 hours, the animal fell unexpectedly on its flank and displayed general clonic reflexes and running movements. The head was retracted into the neck, corneal reflex was weak, and the reflexes of the extremities were also weakened. In this phase, pulse and respiration were still normal; the spasms lasted 1 to 2 minutes and were followed by flaccid paralysis. The animal lay on its flank until the next spasm and did not rise again. The convulsions, every 15 minutes, became constantly weaker; then a dyspneal state developed with opisthotonos. Convulsive inspiratory movements occurred; one-half hour after the first attack, the breathing stopped, but the heart continued to beat for a short time.

We also tested the toxicity of the ricin prepared by us in guinea pigs: The lethal dose used was 10 mg per kg body weight; a short time after the injection of the solution, the animal fell on its flank and displayed convulsive movements of the head and attacks of dyspnea; death occurred after 72 hours.

At the end of 1891 Ehrlich demonstrated that animals may be experimentally immunized against ricin by injecting the poison into them in an appropriate manner, thus producing an antiricin. Rats and rabbits are well suited for these experiments and, after appropriate treatment, they will support 1,000 times the initial dose, or more, even when the ricin is introduced intravenously.

The antiricin has good resistance to trypsin when heated to 60° C for 2 hours or HCl and pepsin for 1 hour. The serum containing antiricin also seems to possess an agglutinin distinct from antiricin, but not yet successfully separated from it.

The experiments of Carmichael demonstrated the presence in ricin of two biological functions, a toxic and an antigenic function, each of which depends on a different part or group of the toxin. He in fact succeeded in detoxifying ricin by treating it with humid heat or with potassium permanganate without destroying its antigenic potency and hence its capacity to immunize.

We wish to state that we are interested in the antigenic property of ricin, and that this property is present in doses infinitely removed from the toxic doses.

We used ricin for the cutaneous reaction tests in the last few patients who came under our observation, among them two of those described above, and obtained a constantly and intensely positive result in all those cases where the reaction was also positive for the seeds and cake of ricinus.

The number of ricinus asthma cases studied by us is 16, of whom three have already been described. We shall now report the principal data of the rest of the cases in a succinct manner.

Case 4: G. Angela, 37, Roncade (Treviso), unmarried, homemaker. For 7 years typical asthmatic attacks. White cell count: 13,000. Leucocytic formula: neutrophils, 57 percent; eosinophils, 10 percent; basophils, 1 percent; lymphocytes, 28 percent; monocytes, 4 percent. Wassermann reaction: negative. Fecal and urine examination: negative. Walcher cutaneous reactions: ricinus cake++++, ricinus leaves+++, ricinus husk+++, ricin+++, ricinus pollen---, corn powder+++, linseed powder++.

Case 5: Olimpia, 44, Meolo (Venezia), unmarried, dressmaker. For 2 years frequent rhinitis with sneezing; rhinorrhea followed by dyspneal crises having the character of attacks, with coughing and emission of a viscid secretion. In July 1944 underwent nasal surgery by a specialist (nature of operation not specified) at the Venice

Municipal Hospital. Fecal and urine tests for Koch bacillus: negative. Hemochromic examination: Hb, 82; red cell count, 4,300,000; white cell count, 8,400; globulin value, 0.95. Leucocytic formula: neutrophils, 67 percent; eosinophils, 6 percent; lymphocytes, 20 percent; monocytes, 7 percent. Thoracic radiography: moderate sclerotic thickening of the left apical pleura accompanied by slight sclerotic symptoms under apex with few opaque nodules in the right middle field; hemidiaphragms mobile; costophrenic sinuses free. Walcher cutaneous reaction: castor seeds+++.

Case 6: Ulderico, 41, Este, married, porter. From age 25 on, during the spring and summer seasons, suffered from dyspneal crises having the nature of attacks, with coughing and emission of viscid secretion, unaccompanied, it seems, by rhinitis. Ear, nose, and throat examination: hypertrophy of the nasal turbinates and multiple crests of the septum. Thoracic radiography: thorax ample; hint of left convex scoliosis of the dorsal superiors; biapical fibrosclerosis; left hilar shadow dense and enlarged; some nodular calcifications under the right hilar region; other calcareous noncolored nodules under the left hilar region; left diaphragm blocked laterally. Heart and large blood vessels: normal. Urine and fecal tests: negative. Wassermann reaction: negative. White cell count: 9,100. Walcher cutaneous reactions: ricinus cake+++, ricinus seeds+++, ricinus leaves+, mixed seeds++.

Case 7: Zanetti Iginio, age 35, Meolo (Venezia), married, laborer. For 1 year suffered from dyspneal attacks with cough and emission of small amounts of trickling viscid secretion; seems not to have been subject to rhinitis. Ear, nose, and throat examination: hypertrophy of the turbinates deviation of the nasal septum with conspicuous respiratory stenosis.

Thoracic radiography: thorax elongated and symmetrical. Slight degree of left hilar adenopathy; primary calcification at the left base. Diaphragms with regular excursions. Urine and fecal tests, negative. Wassermann reaction, negative. White cell count, 8,600. Walcher cutaneous reactions: ricinus cake++++, fresh ricinus seeds++++, bark of ricinus tree++++, shell of ricinus seeds+++.

Case 8: B. Albino, age 37, Musile di Piave (Venezia), married, farmer. From age 28 suffered from bronchitis of an asthmatic form. In December 1942, suffered dyspneal attacks with cough and viscid sputum; in September 1943, other dyspneal attacks preceded by rhinitis (rhinorrhea, sneezing). Ear, nose, and throat examination negative. Thoracic radiography: thorax regular; biapical fibrosclerosis. Some micronodular calcifications are distinguished at the right apex. Some fibrous striations in the right subclavian. Reinforcement of the hilar shadows. Diaphragm with regular excursions. Urine and fecal tests, negative. Wassermann reaction, negative. White cell count, 4,600. Leucocytic formula: neutrophils, 62 percent; eosinophils, 4 percent; lymphocytes, 34 percent. Walcher cutaneous reactions: strongly positive for ricinus cake and seeds.

Case 9: B. Teresa, age 61, Grisolera, married, homemaker. For 12 years, from March to October, subject to dyspneal attacks with cough and viscid catarrh, almost always preceded by rhinitis with rhinorrhea, sneezing, nasal itching. Ricinus is intensely cultivated in the area where patient lives. Ear, nose, and throat examination: deviation of the septum; left middle turbinate hypertrophic. Thoracic radiography: partial covering of the bases, especially on left. Slight left hilar adenopathy; heart with normal diameters; aortic sclerosis. Urine and fecal tests, negative. Wassermann reaction, negative. Hemochromic test Hb, 100; red cells, 4,850,000; white cells, 8,300; globulin value, 0.96. Leucocytic formula: neutrophils, 66 percent; eosinophils, 6 percent; lymphocytes, 26 percent; monocytes, 2 percent. Walcher cutaneous reactions: ricinus cake++, ricinus seeds++.

Case 10: S. Maria, age 38, Portogruaro, housewife. For 8 months has suffered dyspneal crises with cough and viscid catarrh, often preceded by rhinitis. Ear, nose, and throat examination, negative. Thoracic radiography: structure and transparency of pulmonary fields, normal. Right hemidiaphragm, hypermobile. Costrophrenic sinuses, free. Fecal and urine tests, negative. Wassermann reaction, negative. Sputum examination, negative for Koch's bacillus. Leucocytic formula: neutrophils, 68 percent; eosinophils, 8 percent; lymphocytes, 23 percent; monocytes, 1 percent. Walcher cutaneous reaction, positive for ricinus cake.

Case 11: B. Giuseppe, age 36, Conegliano Veneto (Treviso), married, workman. Since June 1945, has suffered continual dyspneal attacks with cough and viscid sputum. The asthmatic state ceases when patient goes a few kilometers from his home area where ricinus is intensely cultivated. Ear, nose, and throat examination: turbinal mucosa of a cyanotic color. In middle meatus purulent exudate. Radiography of the paranasal sinuses, nonhomogeneous blocking of all paranasal sinuses, more intense in the maxillaries: in the inferior external part of the right maxillary sinus opacity with clear boundaries having the character of cysts of the mucosa. Thoracic radioscopy, negative. Urine and fecal examinations, negative. Wassermann reaction, negative. Leucocytic formula: neutrophils, 72 percent; eosinophils, 6 percent; lymphocytes, 18 percent; monocytes, 4 percent. Walcher cutaneous reactions: all Poaceae tested+++, including Poa pratensis, Trivialis annua, Cynosurus elegans, C. cristatus, Festuce pratensis, rye, Agrostic alba, Brachypodium pinnatum, Hordeum bulbosum, Trisetum flavescens (couch grass), Gaudinia fragilis, Holcus lanatus (velvet grass), Bromus mollis, Lolium italicum, Agropyrum caninum, Sorghum lalepense; all Quercaceae tested+++, including Quercus cerris, Quercus ilex, Quercus Libani, Quercus pseudosuber; ricinus seeds+++, ricinus cake+++, ricinus oil---, ricinus leaves+, ricinus pollen---, non-dialyzed ricin++++, dialyzed ricin++++. P. K. passive transport test: intensely positive for ricin and ricinus seeds and slightly positive for ricinus cake; the control carried out at the site not treated with the serum of the patient turned out negative. After inhaling dialyzed ricin, the patient immediately presented characteristic bronchial asthma attacks. After washing with soap made from castor oil the patient presented typical asthma attacks.

Case 12: B. Gina, age 42, Roncaglia, homemaker, married. Patient had bronchial asthma for 12 years. Walcher cutaneous reaction: ricinus seeds++++.

Case 13: G. Carmela, age 35, Musile di Piave (Venezia). Patient has had asthmatic attacks since September 1945. Walcher cutaneous reaction: ricinus seeds++++, linseed flour++.

Case 14: F. Elvira, age 45, Roncade, married, farmer. Patient has asthmatic attacks from the moment the ricinus is being gathered. Walcher cutaneous feed++++, linseed flour+++, corn powder+++, Agropyrum caninum+++, Ambrosia trifide+++, Sorghum halipense +++, Ambrosia arthemisia+++, Zea mais++.

Case 15: D. Luigi, Campiglio dei Berici (Vicenza). Walcher cutaneous reactions: ricinus seeds++++. Poaceae: Melica ciliata +++, Dactylis glomerata+++, Cynodon Dactylon+++, Anthemis tinctoria+++, Lolium perenne++, Hordeum bulbosum+++, Artemisia absinthium++, Xanthium strumarium,++, Bromus mollis+++, Anthemis cotula+++. Rosaceae: Tilia argentea+++, gladiolus gandavensis++, camellia japonica++, Acacia dealfata+++, Acer negundo +++, Agave nigra+++, Robinia psaudoacacia+++, Paeonia hybrida +++, Ranunculus repens+++. Cucurbita Pepo+++, Salix alba+++, Chamaedorea oblongata++, Populus oblongata++, Populus angulata ++++, Populus nigra++++, Aesculus hippocastanus++++, Quercus cerris++++, Quercus ilex++++, Quercus Libani++++, Quercus macrocarpa++++, Quercus pseudosuber++, Papaver somniferum +++, Phoenix excelse+++, Papaver Rhoeas++, Magnolia grandifolia ++, Fraxinus ornus++++, Betula alba++++, Tulipa silvestris++++, Acer californicum+++, Plantanus orientalis++, Ulmus campestris++, Castanea vesce++, Tilia platiphilla++, Buxus ballarica++, Bignonia Tweediana+++, Beta vulgaris+++, Ilex agrifolium+++, Oenothera lamarciaxa+++, Genista canadensis+++, Cequoia sempervirens++, Punica granatum++++, Paulownia imperialis+++, Paliurus australis +++, Hipericum perforatum++, Hydrangea quercifolia+++, Alnus incana+++, Tropeolum maius++, Datisca cannabina+++, Acer Negunda++, Tilia argentea++.

Case 16: M. Antonietta, age 40, Conegliano Veneto, housewife. From age 28, that is, since 1934, has suffered from bronchitis accompanied by moderate dyspnea; this dyspnea is continuing with periods of exacerbation which the patient cannot attribute to any cause, and with periods of greater though not complete tranquility, especially when she goes away from her place of residence. From July 1944 on, increasing contact with ricinus causing true and typical asthmatic attacks with cough, feeling of suffocation, viscid sputum, preceded by rhinitis with sneezing and nasal itching. During the winter season the symptomatology is attenuated, only to reappear in an increased form during the summer. Thoracic radiography: the pulmonary fields appear hyperilluminated by a light degree of emphysema. The right hilus appears more exposed than normal due to the displacement of the heart toward the left, where a light degree of pleuritis is observed in the form of a partial blocking of the costophrenic sinus and slight interlobar thickening; in the left subclavian a few micronoduli of medium and intense opacity (in sclerosis or calcified) with a few small hilar calcifications. Urine and fecal examination, negative. Wassermann reaction, negative. Sputum examination, negative for Koch's bacillus. Basal metabolism, +20 percent. Hemochromic examination: Hb, 72: red cells 3,920,000; white cells, 4,600; globulin value, 0.92. Leucocytic formula: neutrophils, 63 percent; eosinophils, 7 percent; lymphocytes, 30 percent. Walcher cutaneous reactions: pollens: Aster ericoides++, Cucurbita Pepo++, Ranunculus ficaria++, Plantage coronopus++, populus angulata++, Quercus Libani Chamaerrps humilis+++, Robinia pseudoacacia++. Powders: vanilla++, kapok++, news print++. Hairs, feathers++. Foods: oysters++, cuttlefish++. Ricinus: seeds++++, leaves++++, cake ++++, powder++++, ricin solution++++, dialyzed ricin++++, pollen−−−, castor oil−−−.

In 83 cases of bronchial asthma hospitalized or examined in an ambulatory manner in our Department since 21 August 1943, the cutaneous reactions for ricinus have been positive in 16, or 19.4 percent. This unusually high incidence must be attributed to the particular circumstances of the war. The excessive restrictions on distribution of fats and soaps induced many families to manufacture fats and soaps from ricinus in whose seeds the oil content is very high (40 to 50 percent), and at the same time the cultivation of ricinus was undertaken in regions where this had not been done before. Many of our patients in fact came from regions where the cultivation of ricinus was intensive.

In eight cases of hypersensitivity, the reactions were positive for other antigens besides ricinus (bullrush in Case 3; corn powder in Case 4; Poaceae and Quercaceae in Case 11; linseed flour in Case 12; birdseed, chicken feed, and other grain powders in Case 14; Poaceae, Quercaceae, and Rosaceae in Case 15; powders, pollens, hairs, and food in Case 16).

According to some authors, multiple hypersensitivity exists as such only in appearance, inasmuch as the patients may be sensitive to agents common to different, but biologically related substances and, in the case of food allergy, to the same products of the digestive process common to different substances.

We used a large number of antigens prepared from ricinus (seeds, peels of seeds, wood, husks, leaves, dialyzed or non-dialyzed ricin, oil, pollen), but could not carry out cutaneous tests in all patients with all the above antigens because at times we were short of material.

All tests for cutaneous reaction with ricin were constantly positive; the reaction, especially in Cases 11 and 16, appeared more intense than the reaction caused by the rest of the antigens from the same group. Naturally, dialyzed ricin furnishes more vivid reactions than the non-dialyzed form because of its higher degree of purity.

The cake, seeds, peel, and husk gave constant and intense positive reactions, whereas the leaves always gave more modest reactions. In explaining this fact, are we to assume the existence of a particular form of multiple hypersensitivity of a group? Or should we rather think of the existence in these different antigens of a single factor present also in ricin? Or could it be that all these antigens contain ricin, though in minimal amounts, which would then represent the antigen common to all members of the ricinus group?

The reactions with pollen and oil have been constantly negative.

In some cases, we attempted to provoke asthmatic attacks experimentally by having the subject inhale from the cake and ricin; the desired result was always obtained, sometimes after about 20 minutes and sometimes immediately (Case 11). In the same particularly sensitive case, the attack was provoked by having the patient wash his hands with ricinus soap.

Similarly positive has been the passive transfer test for hypersensitivity according to Prausnitz-Kustner.

Age: Our patients were most frequently attacked during adulthood. Most subjects were around 40 years of age; one was 54, and one, 61. This agrees with the general concept that, in infancy, the alimentary causes prevail and the inhalatory causes are few: with increasing age, one loses one's sensitivity toward food substances and acquires instead a sensitivity toward inhalable substances. The first condition is related to the frequency of digestive disturbances and the greater fragility of the intestinal epithelium.

Environment: Many patients came from the same region or locality where ricinus cultivation was extensive, and the probability was high that the families living in the area would use ricinus for the purposes already indicated. (Pieve di Soligo and Conegliano were the homes of Cases 1, 11, and 16; Meolo Musile di Piavo, Grisolera, and Roncade are all adjacent communities of Cases 4, 5, 7, 8, 13, and 14; and Portogruaro was the home of Cases 2 and 10.) In fact, the knowledge that the asthmatics who came under our observation had come from the above localities actually served to orient the cases rapidly.

The geographical distribution of allergic diseases is especially well known in the case of pollinoses; in America, where these illnesses are very frequent, geographic charts have been compiled for diagnostic guidance in proper desensitization treatment.

Sex: The two sexes were attacked by the disease to an equal extent.

Eosinophilia: Generally there has been an increase, though not a conspicuous one, in the number of eosinophils which, in Case 3, reached 24 percent and in Cases 2 and 4, 10 percent. This, however, is more frequent in the pollinoses, and it is known that it may decrease in periods in which no attacks occur. At the beginning of the attack, the eosinophils decrease in the circulating blood, and there occurs a medullar stimulation of the production of neutrophils, which are more easily producible; then, at the end of the attack the production of eosinophils, too, is stimulated. The easinophilia begins with the onset of the first respiratory symptoms and rises until the third week. A permanent lymphocytosis is not a rare occurrence in asthmatics. Some believe that the eosinophilia is a local and not a medullar phenomenon; others maintain that it is also a medullar phenomenon (De Renzi).

We must next consider that here, as in the cases described by Ancona of epidemic "Pediculosis ventricosus" asthma, we have had an epidemic form of ricinus asthma in a region (Grisolera and vicinity) where, because of the necessities of war, ricinus was cultivated extensively, and soap was prepared at home from castor oil. Many individuals, the majority of whom had never exhibited allergic manifestations, displayed a sensitivity, most probably provoked by means of a respiratory or cutaneous route, to an agent to which they were particularly exposed. We, therefore, visited this region and performed the cutaneous reaction indicated since the anamnesis made us suspect ricinus as the probable cause of the morbid symptomatology in question.

We report below our observations:

1: G. Pietro, age 39. Has cultivated ricinus in the vicinity of his own house for 3 or 4 years. During the last 2 years has taken to making soap at home and, coinciding with these occasions, has had typical asthmatic attacks. Relates that even the presence of soap in the room provokes in him a state of dyspnea, which disappears when he goes away from the substance. Cutaneous reaction: positive for dry ricin and ricin in solution, leaves, and ricinus seeds.

2: B. Aldo, age 26, tailor. Does not cultivate ricinus, but has bought seeds and has been making soap for 2 months. Under these circumstances, he has experienced an outbreak of asthma, which still persists, though in a more attenuated form, even when he is away from the substance. Cutaneous reactions: Intensely positive for ricin, leaves, ricinus seeds, and even for ricinus pollen. His family members who have participated in the soap-making do not have asthma, and the cutaneous reactions performed on them are negative.

3: B. Antonio, age 54. Has been cultivating ricinus for 8 years; during the last 2 years has devoted himself to the husking of seeds in order to make soap. In coincidence with this operation he experiences asthmatic attacks. The dyspneal state lasts for a few days even after he is removed from the substance. Cutaneous reactions are positive for ricin and seeds.

4: P. Emma, age 22. Had asthma 3 years ago during the husking of castor seeds. Since then has not worked with seeds, and has had no asthma attacks. The soap does not disturb her. Cutaneous reaction is intensely positive for ricin and leaves.

5: M. Oliva, age 33. Has cultivated ricinus for 8 to 10 years, but the asthmatic attacks started only when he began making soap and personally husked the seeds. Cutaneous reactions: ricin+++, leaves and seeds+++.

6: B. Emma, age 16. Has been cultivating ricinus at home for 4 years. She had not experienced any asthmatic attacks during the previous years while making soap; a few days ago, however, she had them while husking ricinus seeds. Started menstruation this year. Cutaneous reactions: all positive.

7: A. Guiseppe, age 49. Asthma occurred for the first time 1 month ago when he started to husk ricinus seeds preliminary to soap-making. The seeds were acquired from neighbors since he himself does not cultivate ricinus. Cutaneous reactions: intensely positive for ricin, seeds, and leaves.

8: Z. Gino, age 7. For 2 years has suffered from asthma, especially during the spring and summer. A few typical attacks have occurred during the manipulation of ricinus seeds for soap-making. He washes with this same soap without experiencing disturbances. Cutaneous reactions: positive for ricin and ricinus leaves.

9: R. Regina, age 40. For 3 months has suffered asthmatic attacks every time she comes in contact with castor seeds or soap. Cutaneous reactions: intensely positive for ricin, less positive for seeds, even less positive for leaves; negative for soap.

10: V. Cirilla, age 43. Has had asthma for 8 years, in the spring and summer, at the time the grain and hay are gathered. Also experiences typical asthmatic attacks in the presence of ricinus seed. Cutaneous reactions: negative.

11: G. Amelia, age 34. For 3 years has suffered asthmatic attacks coincidentally with work on ricinus. Cutaneous reactions: positive for ricin; negative for the other members of the group.

12: C. Albina, age 32. For 3 years has suffered from asthma only when working with castor seeds. Cutaneous reactions: very uncertain for ricin and soap, and absolutely negative for the other members of the group.

13: T. Angelo, age 38. For 2 years has suffered from asthma when working with castor seeds, and is affected even when he is some 20 meters from an area where ricinus is being processed. Does not use the soap made from ricinus for personal hygiene, nor has he had asthma when taking the soap in his hand. In his family, the 15 or so persons who participate personally in the processing of ricinus seeds are not affected by asthma. Cutaneous reactions: intensely positive for ricin, somewhat less positive for the seeds, and even less positive for the leaves. Of the family members examined only one had a dubious and slight positivity for ricin and seeds.

14: C. Primo, age 25. Asthmatic attacks started about 20 days ago when he began to husk ricinus seeds. Cutaneous reactions: negative.

Thus, we examined asthmatic subjects in whom the anamnesis made us think of ricin as the probable cause and in whom the cutaneous reactions proved positive in all but three cases. The family members were negative on the basis of both anamnesis and the cutaneous reactions to pollen.

The positivity of the cutaneous reactions was more intense for ricin, whether in a powdered or solution form, a little less intense for the seeds, and even less intense for the leaves. Negative reaction was obtained with the cake and the soap (in some cases rather dubious). A few patients reported that they experienced asthma with ricinus soap either when using it for washing or when keeping it in the room.

* * *

Our final intention was to investigate the allergic reactivity toward ricinus in workers in plants manufacturing oil.

For this purpose, we visited the factories of Gobetti at S. Pietro di Legnano and that of the Castor-Oil Company of Lower Verona at Castagnaro di Verona.

The seeds arrive in a decapsulated form; they are heated to 40° to 50° C for an hour, then pressed mechanically. When a certain quantity of oil has been pressed out, the residue is subjected to the action of a second press, then again heated, ground, and pressed. The residue from these operations, after the oil has been pressed out, is ground, and the resulting cake is used for fertilizer.

With the permission of the owners, workers in the Gobetti factory, some of whom had worked there for about 30 years, were tested for cutaneous reactions with seeds, leaves, cake, dialyzed and non-dialyzed ricin, pollen, and oil. These tests were negative for each worker. In agreement with these findings, the anamnesis was also negative. Analogously, the anamnesis obtained from the workers of the second establishment (with the aid of the physician who attended the plant for the past several years) was also negative. For this state of affairs we believe the following explanation may be given: the mechanical processing is such that not the smallest particles of seed are released to come in contact with the mucosa of the respiratory passages; whereas, in the epidemic described by Lucchese the manipulation of the husks in the establishment in question made it possible for a portion of minute particles to be dispersed in the air over a longer or shorter distance, thus sensitizing the mucosa of the respiratory passages.

* * *

Insofar as therapy is concerned, we believe it appropriate to make the following observations:

The removal of the allergen remains fundamental. Specific desensitization therapy has often been found dangerous since we are dealing with a substance of high allergic potency. We know of cases in which the desensitization by means of cutaneous reaction produced serious states of shock; one of our colleagues reported a case in which the intradermic injection of small amounts of powdered castor seed led to severe anaphylactic phenomena. In particular, we advise against Bray's violent shock method by means of intermuscular injection of the substance.

We must always keep in mind that the allergic dose is infinitely smaller than the toxic dose and that the former is not the same for all persons, but varies according to individual sensitivity.

If one wishes to prepare a vaccine, one should perform intradermal reactions by means of increasing dilutions of the allergen until a dilution is reached that no longer gives a reaction; administer this dilution in an initial dose of 0.10 cc, add 0.10 cc to each successive injection given at intervals of 5 days between injections until a dose of 1 cc is reached. Then proceed to the next lower dilution; that is, the dilution that, when introduced intracutaneously, still gives a positive reaction. Again start with an initial dose of 0.10 cc and continue with increasing multiples of this dose with each successive injection given at 5-day intervals.

SUMMARY

The authors describe 16 cases of ricinus asthma, 20 percent of the patients hospitalized for bronchial asthma in the First Division of the Padua Municipal Hospital during the recent war and the period immediately following; they ascribe the cause of this unusually high incidence to the increased contact with castor beans used in the home production of soap and fat necessitated by war-time restrictions on normal imports.

The authors also describe an epidemic of 13 cases of ricinus asthma in a region where ricinus plant was extensively cultivated (Grisolera di Venezia); they visited two castor-oil plants in the Basso Veronese and reported the reactivity to ricinus of the plant workers. The cutaneous reactions from tests performed on them were negative for seeds, leaves, cake, dialyzed or non-dialyzed ricin, pollen, and oil.

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BRONCHIAL ASTHMA AND ALLERGY DUE TO CASTOR BEAN POWDER

By Guiseppe Lucchese

In the last months of 1948, I observed in the municipality of Figline Valdarno an unusually high number of cases of bronchial asthma. I considered the number unusually high because, in the 16 years of my professional activity in this region, I had heretofore treated only a few asthma patients, all of whom had histories of prior bronchial illnesses and of rare incidents of true asthmatic attacks.

Almost all of the 11 cases I observed in this area between September and December of 1948 had no previous history of respiratory ailments. Moreover, during the same period, cases exhibiting a more attenuated form of asthmatic syndrome were seen by other health officers practicing in this region; however, I cannot discuss any of the latter cases since I had no direct contact with them.

The majority of my patients had been hospitalized once or several times for varying periods of time. All cases were subject to sudden typical attacks of bronchial asthma. The attacks generally lasted a few hours and recurred at irregular intervals ranging from a few days to a few weeks, always with the same symptoms of tightness of the throat, shortness of breath, suffocation, and insistent coughing with mucus production, rather sparse at first, but abundant toward the end.

A fact to be emphasized is that the attacks occurred almost contemporaneously in all patients. They would be well, when suddenly, for example during the night, all or nearly all of them would experience the asthmatic phenomena in a more or less accentuated form. The district physician would be called by a number of these patients at the same time on account of the sudden asthmatic attacks, or five or six of these patients would have to be taken to the hospital at the same time, suffering from grave attacks of dyspnea.

The unusual number of persons struck by asthma and the contemporaneity of the onset in the different patients indicated to me that a particular agent was responsible for the provocation of the syndrome and this agent must be the same for all patients.

I learned that some of the workers at the oil-extraction factory of "S.T.O.V.A." had exhibited various disturbances: one of them had frequent attacks of dyspnea and irritation of the respiratory passages with abundant nasal secretion and conjunctivitis with profuse lacrimation. I verified that these attacks took place when castor beans were processed but not when other products, such as olive seeds, were processed.

Furthermore, I ascertained that the asthmatic patients not attached to the S.T.O.V.A. plant lived or worked, in most cases, in the vicinity of the factory—a few hundred meters—and that their symptoms, too, coincided with the processing of castor beans. Hence, I concluded that the probable cause of the syndrome should be sought among the substances handled in this factory and that of these substances castor beans were particularly suspect.

From a visit to the plant and from information furnished by the factory personnel, I learned that the plant, by special processes, extracted oils for industrial use from castor seeds delivered from other regions in the form of compressed briquettes. At the plant they were pulverized mechanically and then treated with petroleum ether to extract the oil. The castor-bean powder passed through an elaborate system of pipes, and doubtless a part of this fine powder was spilled and thus transported by air currents for longer or shorter distances from the plant.

Knowing that bronchial asthma is the most common of maladies in which allergic sensitization is the cause of onset, I thought that probably it was the castor bean dust to which the allergization must be attributed.

I spoke of my findings and my suspicions regarding the origin of the syndrome to Prof. Ignio Spadolini, Director of the Institute of Physiology of the University of Florence, which has a special competence in the field of allergic diseases and in the preparation of the antigens and antiallergic vaccines. Following his advice, I prepared antigens from samples of the castor beans at various stages of manufacture and then performed cutaneous tests according to Walcher's method. I produced two scarifications a few cm apart in the anterior part of the arm of each patient, placing on one of these scarifications a drop of antigen prepared from the whole seed and on the other a drop of antigen prepared from the powder of castor beans. After 10 to 15 minutes, a very evident positive reaction occurred in both scarifications—the formation of a large wheal, erythema of the vicinity, and lymphangitis—making the reaction site resemble a large ameba with more or less protruding pseudopodia. In some cases, urticaria spread rapidly to other parts of the body, and sensations of pruritus and heat occurred at the site of the reaction. In two patients, I performed simultaneously the cutaneous and the intradermal tests. Reactions were positive and obviously comparable. One of these patients suffered a most severe attack of dyspnea about 12 minutes after the injection of the antigen.

For control purposes, I performed the cutaneous reaction test in four other patients treated in the hospital for other ailments; one of these patients was suffering from arteriosclerosis; another, a woman, was hospitalized for fracture of the femur and, in addition, had suffered for many years from bronchial asthma; the third patient had colitis; and the fourth, chronic bronchitis. In all four cases the tests were negative with not even a minimal reaction observable.

For definite confirmation, I gave one of the patients the passive local transfer test according to Prausnitz-Kustner, as recommended by *Frugoni. I obtained from* a patient in whom the cutaneous reaction was positive a few cc of blood and injected a drop of the serum obtained from this blood into the dermis of the arm of a healthy subject. After 24 hours, the Walcher cutaneous reaction test on the same site was clearly positive.

The test of positive transfer, according to most authoritative authors, offers a confirmation of the specificity of the allergy. Since in our case the test was positive, it appeared that we were dealing with a true allergy to castor beans.

Both antigens, the one prepared from castor-bean powder treated with petroleum ether and the other prepared directly from whole castor seeds, gave the same positive results with no difference in the intensity of the reaction. This means that the action of the solvent petroleum ether is not necessary for the development of allergic effects by castor-bean powder and, on the other hand, that the solvent does not deprive the castor-bean powder of its allergizing potency.

The causative agent of the asthmatic syndrome of our patients thus having been identified, I proceeded to the preparation of the appropriate specific vaccine. Treatment consisted of administering subcutaneous injections in increasing doses in the customary manner; in general, it was beneficial to all patients.

And now, briefly, the most salient data of the cases observed are given:

Case 1: S. T., age 35, Figline, dealer in skins and hides. Admitted to hospital on 11-2-48.

For about 3 months from August 1948 patient had dyspnea with coughing attacks and profuse expectoration. The attacks were preceded by abundant secretion of nasal mucus and lacrimation. They occurred frequently, and also at intervals of 10 to 12 days during which period the patient was well and had no complaints whatsoever. He remarked that whenever he had to go away from Figline for occupational reasons he was free from complaints. At the start of the illness he was subjected to various medical treatments, calcium and intravenous ephedrine, intravenous novocain, antiasthmatics, and nonspecific antiallergics. He was then hospitalized at a nursing home in Florence for about 15 days. There, among other treatments, he was tested for allergic reaction with an antigen prepared from hide; the result was negative. Since the patient was in constant contact with hides, a vaccine was prepared from the same hide. There were, however no resulting benefits for the patient. Thereupon, he was placed on penicillin therapy, again without any results worth mentioning.

We performed Walcher's cutaneous reaction test with an antigen of castor bean treated with petroleum ether and with an antigen of the whole ricinus seed. Both gave a strong positive reaction with a projecting lesion 2½ x 3 cm in diameter with numerous lymphangitic prolongations, an erythematous halo around the site, itching, and sensation of heat. In addition, there was a moderate attack of dyspnea and urticaria, the latter originating at the site of the cutaneous reaction and quickly spreading to the chest, the face, and the rest of the body. These phenomena lasted for a few hours.

On the basis of the positive test obtained with a ricinus antigen, a specific vaccine was prepared by means of which a definite improvement was effected in the patient's condition.

Case 2: B. G., age 38, Figline, porter. Admitted 11-17-48. Father died of pneumonia. Patient had no prior disease worth mentioning. On September 28, 1948, he experienced his first attack of dyspnea with coughing and abundant expectoration. He was treated for bronchial asthma with intravenous novocain injections, ephedrine syrup, and calcium thiosulfate. There was no improvement.

Cutaneous reaction with the two antigens was positive as in Case 1. Treated with a specific vaccine, he improved.

Case 3: C. P., age 40, Figline, glazier. Admitted 11-12-48.

Father died of arteriosclerosis. Patient had no prior disease worth mentioning. On October 17, 1948, he experienced his first attack of dyspnea with coughing and abundant expectoration. From then on, he had periodic asthma attacks. No improvement was effected with intravenous novocain, generic antiasthmatics, intravenous, calcium thiosulfate, or penicillin.

Cutaneous reaction was positive with both antigens. Specific vaccine therapy brought about considerable improvement.

Case 4: P. P., age 47, Figline, mason, worker at "S.T.O.V.A." Admitted 11-9-48.

Father died of neoplasia; mother died of pneumonia. Patient had no prior diseases.

He related that even during the first few weeks after work had begun at the plant with castor beans, he had respiratory difficulties and lacrimation and that after a few more weeks he suffered an asthmatic attack. Thereafter, he had further attacks at periodic intervals with coughing and abundant expectoration. There was no improvement with antiasthmatics or specific antiallergics, such as calcium thiosulfate.

Cutaneous reaction with the two antigens was positive. Treatment with vaccine prepared from the antigens produced sensible relief.

Case 5: M. G., age 68, Figline, worker. Admitted 10-19-48.

Father died at 88 and his mother at 82, of old age. Patient had no prior history of illness. On August 15, 1948, he experienced his first asthmatic attack. A few hours before the attack, he had gone to the "S.T.O.V.A." plant to visit a worker injured on the job. From that day on he suffered frequent attacks of dyspnea. Ephedrine syrup and calcium thiosulfate treatment did not afford relief.

Cutaneous test with antigen taken from ricinus powder treated with petroleum ether and simultaneous intradermic test with antigen prepared from untreated ricinus seeds were administered. After about 10 minutes there was a typical asthmatic attack of a rather severe and alarming nature, which subsided in about a half hour after injections of adrenalin and inhalation of oxygen.

There was a positive local reaction with extensive formation of characteristic lesions. After treatment with specific vaccine, the patient improved.

Case 6: F. I., age 20, of Figline, laborer. Admitted 11-19-48. Patient had no prior history of disease. On October 9, 1948, he experienced his first asthmatic attack with dyspnea and coughing with expectoration. From then on there were intermittent attacks of the same type. The usual antiasthmatic and generic desensitizing agents gave temporary improvement.

Cutaneous reaction was positive with both antigens. Specific vaccination produced sensible improvement.

Case 7: L. R., age 35, Figline, mechanic. Admitted the first time on 9-25-48, then again in October and November.

Father, who had a cardiac condition, died of pneumonia; mother died at age 51 of gastric neoplasia. In 1944, patient had pararenal attack. On September 10, 1948, he experienced his first attack of dyspnea with coughing and abundant expectoration. From then on he had frequent attacks, with complete wellbeing between attacks. He was treated with the usual generic antiasthmatics, then sulfonamides, shock, and penicillin; attacks recurred with the same intensity as before.

Cutaneous test performed as in preceding cases gave immediate positive reaction. Treatment with specific vaccine produced some improvement in that subsequent attacks were less intense.

Case 8: F. S., age 49, Figline, clerk. Not hospitalized.

From October 10, 1948, every 3 to 4 days he had dyspnea attacks of an asthmatic nature with sensations of choking in the throat, shortage of air, and coughing with abundant expectoration. He divided his time between Figline and Florence; attacks occurred, however, only in Figline. Treatment with various generic antiasthmatics was unsuccessful.

Cutaneous test performed on December 3 with the two antigens was positive. Specific vaccine therapy effected improvement.

Case 9: C. G., age 45, Figline, glazier. Not hospitalized.

Patient had no prior history of illness. On November 19, 1948, he experienced his first typical dyspnea attack, which recurred at intervals. He was treated with sulfonamide and aspecific antiasthmatics.

First cutaneous test (Walcher) on December 16, 1948, was negative. Since the asthmatic syndrome persisted with attacks similar in nature and coinciding in time with those of the previous patient, a new cutaneous test was carried out on February 22, 1949, which this time was clearly positive.

In this patient the Prausnitz-Kustner passive local transfer test performed as described above gave a positive result. Specific vaccine therapy brought relief in that the dyspnea attacks became less severe.

Case 10: R. I., age 43, Figline, peddler. Admitted 12-7-48.

Patient began having dyspnea attacks on September 27, 1948, with feelings of shortness of breath and with coughing, which at first was dry, then became profusely mucous. Rather frequent attacks lasted a few hours. Treatment with nonspecific antiallergics was without notable result. Because of the nature of his work patient could be away from Figline, and during these periods he was free of attacks.

Positive cutaneous reaction. Treatment with specific vaccine effected improvement.

Case 11: V. F., age 56, Figline, worked at "S.T.O.V.A."

Patient experienced his first attacks of dyspnea around August 20, 1948, shortly after plant had started work with ricinus seeds. Afterwards, he had frequently recurring attacks. It is to be noted that this patient exhibited a concomitant oculo-rhinitis in addition to the asthmatic attacks. When he was away from the plant, his complaints ceased. Similarly, they disappeared when seeds other than those of ricinus were being processed at the plant (olives, grapes, etc.).

He was hospitalized in November 1948 in the Medical Department of S. Maria Nuova in Florence (Director: Prof. Micheli). In the therapy, aerosols of synthetic antihistaminics were used with immediate but not lasting disappearance of the asthmatic symptomology. During his stay he was made to inhale, as an experiment, ricinus powder, which immediately produced an asthmatic attack accompanied, as usual, by profuse lacrimation and marked irritation of the nasal mucosa (oculo-rhinitis).

The cutaneous tests with the ricinus antigens were negative. The negative reactions notwithstanding, because of the manner of onset and the characteristic circumstances of the manifestations, we felt it very probable that even in this case we were confronted with an allergy caused by castor seeds. For this reason we administered a vaccine prepared from ricinus.

Even this patient benefited greatly from the treatment.

And now, a few brief considerations.

In the first place, there does not seem to be any doubt that all these illnesses are the effects of the same morbid syndrome whose pathogenesis is related to a single causative factor, the allergizing action of castor-seed powder. The date inferred from the manner of precipitation of the syndrome and the knowledge of the circumstances in which the asthmatic attacks manifested themselves lead logically to this conclusion. Results of positive cutaneous tests and the passive transfer test confirm this inference.

Only in the last case was the cutaneous reaction negative. Nevertheless, in spite of this sole unconfirmed test as against the positive reactions of the other 10 cases, I maintain that even in this case the causative factor was the allergizing action of the castor beans. Both the anamnesis and the symptomology of this patient lead to this conclusion. As mentioned above, this patient noted the first symptoms as soon as he worked with castor seeds. Hence, this could be one of those cases in which, according to Frugoni, one can make a diagnosis only on the basis of an accurate clinical history since, as in the case in question, by using tests one risks provoking the experimental recurrence of the morbid picture.

Of the 11 patients, only 2 were attached to the plant and exposed to direct contact with the allergizing substance—2 out of about 25 persons working there—whereas the other 9 patients were not connected with the plant. The latter patients worked or lived between 200 and 800 meters from the plant, indicating that the allergizing substance in the form of minute grains of powder is capable of traveling a few hundred meters.

Atmospheric factors also may play a part in the allergization. The residential area of Figline is in the near center of a valley that in ancient times constituted the bottom of a lake. It is surrounded on nearly every side by mountains, and the atmosphere remains humid and stagnant with persistent low clouds, especially during the autumn season.

Cases of castor-bean allergy are known and have been described time after time during the past few decades, especially by American authors. In Italy, too, Sangiorgi of Milan and Scimone of Padua have informed me by letter of their observations of castor-bean allergy.

Sangiorgi, who is about to publish a book on the subject, includes among the occupational allergies those caused by castor beans; he cites cases of workers in plants engaged in the manufacture of castor oil, of pharmicists handling the substance, of aeronautical personnel who employ castor oil as a lubricant, and finally of workers in plants producing fertilizers containing castor-bean powder. Sangiorgi does not describe the exact symptoms of these patients. As for the pathogenic modalities of the sensitization, only the last group, the workers attached to fertilizer-manufacturing plants, present analogies to the cases discussed above. In any event, the investigations of this author revealed that the allergic phenomena are manifested only by those workers who have had direct and immediate contact with the allergy-producing substance and not by elements of the population-at-large, as in my study.

Scimone observed an epidemic of asthma caused by castor seeds, but his cases involved cultivators of castor beans, whereas my cases were workers at an oil-processing plant. I have no direct knowledge of the process used in this plant for the treatment of castor beans, but it would be interesting to know whether in the method used for the extraction of oil there was a phase in which the castor seeds are crushed and reduced to minute dry particles capable of remaining suspended in the air. I believe that the method used for the extraction of the oil in Scimone's cases is different from that used in our plant for extracting residual oil. There probably exist other plants in Italy in which the residual oil in the seeds is extracted by the same process as used in Figline Valdarno. In any case we do not know if, in connection with these operations, cases of asthma have been observed among the workers or the outside populations; it could be that there were no such cases, but it could also be that some isolated cases had gone unobserved, with the true nature of the illness remaining unrecognized.

Observations very similar to mine may be found in reports of studies by certain American authors who speak specifically of asthma caused by castor-bean dust.

Bernton, who had been concerned with the problem at the end of 1923, returned to it in 1945. He described cases of allergic bronchial asthma in workers engaged in operations involving castor seeds. Even more interesting is the observation of Figley and Elrod. These authors observed in the state of Ohio a true endemic asthma caused by castor seeds—30 cases among workers involved in manufacturing processes, persons living in the vicinity of the plant, and school children.

Other authors, including Blank, Coulson et al., Spies, Zerbst, Stienen, Buton, Bennett and Schwartz, and Ratner, attempted by means of laboratory research or a study of clinical cases to determine the sensitizing power of ricinus—the oil, leaves, seeds, and powder—and the respective allergic manifestations.

The possibility of the incidence of bronchial asthma of allergic nature among persons working in castor-seed processing plants and among neighboring populations, first described in the United States by Figley and Elrod, is confirmed in Italy by my own study. Actually, I came upon the study of Figley and Elrod after I concluded the investigation of my own clinical cases.

In addition to its theoretical importance, this study is important for practical reasons; it points out problems that concern occupational medicine and legal medicine.

I noted how treatment with generic antiasthmatic and antiallergic agents had a limited effect, a temporary amelioration. Better results were obtained with specific vaccines; that is, when the type of allergen involved was known. In regard to the practical aspects of desensitization by means of the vaccine prepared from the allergizing substance, one should keep in mind the possibility of a spontaneous vaccination. Such spontaneous vaccination in some of the workers in the plant and in various segments of the population-at-large probably accounted for the symptoms observed during the first few months after operations had started at the plant—symptoms very similar to those noted in our actual cases, but on a much more attenuated level, which decreased until eventually nearly all the symptoms disappeared. In regard to treatment and prophylaxis other than desensitization of the stricken persons, the allergizing substance should be diffused into the surrounding area as little as available technical means permit. Preventive measures are warranted by the fact that very small quantities of the allergens in the allergizing substance are able to precipitate an attack, and also that such an attack would occur much more rapidly from a larger concentration of noxious substance.

The concept that a certain definite amount of allergen is needed for the precipitation of an attack is not new; the work of the Dutch investigator, Storm van Leeuwen, is based on it. In certain low-lying, humid zones of Holland where the causative agent of an endemic outbreak of asthma was found to be certain microscopic fungi (aspergilli) suspended in the air, Storm van Leeuwen obtained good results by placing his patients for many hours, both during the day and especially while asleep, in special chambers provided with filtered air. He believed that in order to precipitate an asthmatic attack the allergizing substance had first to be present in a threshold quantity in the organism.

Frugoni and Melli, taking up this concept, advised, without having recourse to the expensive apparatus of the Dutch pharmacologist, the construction of special chambers in which the patients sleep in an open, fresh atmosphere and in which there are no potential receptacles for the accumulation of powder. The patients thus absorb as little of the allergizing substance as possible, at least during the night; in the remaining hours of the day, forced as they are to move about, they will find it difficult to inhale a sufficient amount of allergenic substance to precipitate an asthmatic state, at least when the case is not one of occupational asthma.

Based on our investigations, we would advise on one hand a specific vaccine therapy and on the other hand the installation of equipment and processes technically expedient so that the allergen-containing castor-bean powder suspended in the air does not attain a concentration capable of precipitating new cases of asthma attacks in already sensitized patients and of causing an outbreak of the syndrome in as yet unaffected persons.

SUMMARY

The author describes an endemic occurrence of bronchial asthma caused by castor-bean powder allergy manifested among the personnel of a plant engaged in the extraction of residual oil from the seeds, and among the inhabitants of the neighboring area. After studying the various cases, dwelling on diagnosis, treatment, and prophylaxis, the author notes how the possibility of such an endemic occurrence poses important problems for occupational and legal medicine.

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ETIOLOGY OF EPIDEMIC ASTHMA IN BAURU

By Ernesto Mendes and A. B. Ulhoa-Cintra

Although the term "epidemic asthma" is inappropriate, it has been used to mean the epidemic-like collective asthmogenic action of an allergen. Ancona(*1*), in 1923, published a study on "epidemic asthma" caused by a cereal parasite, *Pediculoides ventricosus;* van Leeuwen et al.(*2*) confirmed the observations made by Ancona.

Since these initial studies, several reports have been made on the collective asthmogenic action of some allergens, one of which is the castor oil plant (*Ricinus communis*). In an epidemic described by Figley and Elrod(*3*) in 1928 in Toledo, Ohio, 30 cases of asthma were proven to be caused by allergy to the dust of the seed husk of the castor oil plant, and 55 other cases were evidently from the same cause. In the description by Grimm(*4*), in 1939, in Germany, 30 cases were studied in which skin tests with the dust of the ricinus seeds were intensely positive.

Identical observations were made recently in Bauru, a city of 60,000 in the State of Sao Paulo, Brazil. On August 11, 1952, the sanitary authorities of Sao Paulo were notified by the doctors of Bauru of the spread of an epidemic characterized by symptoms of violent dyspnea of an asthmatic type that usually began suddenly and did not respond to epinephrine or aminophylline. By August 14, 150 cases had been reported, and 9 deaths were attributed to the epidemic. All sanitary resources of the State were mobilized by the Secretary of Health, aided by the Butantan Institute and the Faculty of Medicine of Sao Paulo. As a result of the alarming reports published by newspapers and broadcast by radio stations both in the country and outside, the Sao Paulo Association of Medicine called a meeting of all interested institutes. The public was informed that special measures were being taken to confine the epidemic and that no new cases had occurred.

Actually, most patients were hospitalized and properly treated with aminophylline, cortisone, and oxygen, and also with aureomycin, as initially, because of the epidemic proportions and severe character of the disease, it was attributed to a pneumotropic virus. Further studies and observations disproved that diagnosis, leaving a tentative diagnosis of tropical eosinophilia because many patients had up to 20 percent eosinophils. To confirm the hypothesis of allergic origin and to ascertain the allergen involved, the specialists and the sanitary authorities asked for a study and examination of all the patients.

MATERIAL

Thirty patients were studied from the allergy viewpoint; 9 were hospitalized in the Hospital das Clinicas in Sao Paulo; 4, in Bauru Hospital; and 17, in the city of Agudos. All except Cases 15 and 16 lived in Bauru. We shall describe only the essential data of allergic interest, such as allergic antecedents, the occurrence of other allergic symptoms besides asthma, influence of locality, result of skin tests, and the experimental reproduction of symptomatology.

Case 1: I. B., 25, single, 477 Rubens Arruda St., Hospital das Clinicas.

Patient had severe asthma from the age of 5 until 20. For 5 years he had shown no asthmatic symptoms except the allergic type. On August 11, he suffered a violent asthmatic attack, which required hospitalization. The first 24 hours he had itching, pharyngitis, palatitis, otitis, and all typical symptoms of allergy. Because of his critical condition, he was transferred to Hospital das Clinicas in Sao Paulo.

Skin tests revealed a strong positive reaction to the bran of the castor-oil-plant seeds (1:100 by scarification) and moderate intradermal reactions to house dust, cotton dust, and air fungi. The passive antibody transference test (with two patients as controls) was clearly positive. The experimental reproduction of symptoms by the described method was definite after 1 minute of exposing the patient to the allergen. The effect lasted 1½ hours despite immediate treatment with cortisone, aminophylline, adrenalin, and oxygen.

Comment: The patient presented skin reactions to other allergens besides "mamona" (castor oil plant) that caused asthma such as the patient had before the epidemic. This patient might continue to have asthma attacks even if the factory stopped manufacturing castor oil.

Case 2: M. S. V., 63, married, 322 Rui Barbosa St., Hospital das Clinicas.

On August 12, for the first time, patient had a violent attack of asthma. Because his asthma was extremely resistant to any of the usual treatments, he was transferred to Sao Paulo. The symptoms of asthma were not preceded or accompanied by other allergic symptoms. He had no allergic history, either personal or family.

Skin tests revealed a strong positive reaction to the castor-bean bran extract; tests with 15 extracts of other seeds and dusts were negative. An antibody transference test proved positive. The experimental reproduction of asthma occurred within 3 minutes after the patient was exposed to direct contact with the castor bean dust. In spite of oxygen, aminophylline, cortisone, and adrenalin treatment, the patient suffered the attack for 2 hours.

Comment: The history of this patient showed neither present nor (past) hereditary allergy. In spite of the apparent absence of allergical susceptibility, he was definitely allergic to castor beans as shown by his skin reactions and the Prausnitz-Küstner proof of the antibody transference.

Case 3: A. F., 24, single, 670 Sao Carolos St., Hospital das Clinicas.

Since the age of 8, the patient has had bronchitis without difficult breathing; since 15 he has had acute asthma with short attacks and long, calm intervals between them. On August 11, he had a violent attack of asthma and was transferred to Sao Paulo. He had no allergic history, personal or family, showed no allergic symptoms during the epidemic except asthma.

Skin tests made with 16 inhalants revealed a strong positive reaction to the castor-bean bran and a negative reaction to other allergens. The experimental reproduction of symptomatology took place after 3 minutes of exposure to allergen. Besides showing the characteristic symptoms of asthma, the patient vomited continuously, as he did also during the epidemic in Bauru.

Comment: Although the patient had asthma since the age of 15, he did not have skin reactions to other inhalants in Bauru. He reacted positively only to the bran of castor bean. As his personal history showed he had bronchitis since the age of 8, probably the patient carried an infective asthma, and would, therefore, be liable to attacks of asthma even without contact with the castor-bean bran.

Case 4: A. F., 20, single, 318 Barbosa St., Hospital das Clinicas.

On August 11, the patient had his first attack of asthma and was transferred to Sao Paulo because of his critical condition. Since the age of 2, the patient had suffered continuous colds with coughing attacks. Prior to his attack of asthma, he had conjunctivitis with acute symptoms. He had no allergic history.

Skin tests with 16 inhalants revealed a strong positive reaction to the castor bran and a slightly positive reaction to cotton dust and air fungi (*Rhizopus* and *Penicillium*). The passive antibody transference test was clearly positive. The experimental reproduction of symptomatology took place after 3 minutes of exposure of the patient to the allergen, and symptomatology persisted for 2 hours.

Comment: Prior to his attack of asthma, the patient had allergic rhinitis. This was also proved by his sensitiveness to dust and air fungus.

Case 5: G. P. C., 33, male, single, 1138 Rio Branco St., Hospital das Clinicas.

Upon his return to Bauru on August 12 after a 15-day stay in Sao Paulo, patient was attacked by asthma on the very night of his arrival. This was preceded for 4 or 5 hours by rhinitis and conjunctivitis of an allergic type. The patient had rhinitis 10 years ago, characterized by excess mucous secretion and sneezing, principally in the presence of dust.

The patient had a strong positive reaction to castor-bean bran and positive reactions to cotton dust, dust, and cereal dust. The test of passive antibody transference was definitely positive to the extract of the castor-bean bran.

Comment: This case demonstrates that patients who had attacks of asthma on August 11 or 12 were allergic to the dust of the castor-oil beans. The identical allergic symptoms manifested by this patient a few hours after his return to Bauru following a 15-day stay in Sao Paulo were also observed by other doctors during the epidemic, and thus the hypothesis of a virus was eliminated.

Case 6: I. C. J., 20, single, 922 Rodrigues Alves, Hospital das Clinicas.

On August 11, patient had his first violent attack of asthma and was transferred to Sao Paulo because of his critical condition. His attack of asthma was not preceded or accompanied by other allergic symptoms. The patient had no present or past allergic history.

A skin test revealed allergy to castor-bean bran only. Other inhalants gave negative results. The passive transference test against the castor-bean bran was definitely positive.

Comment: In this case, allergy was manifested only to castor beans. The patient had never had other allergies, and his family history was also negative. All these facts suggest the potency of the allergen contained in the husk of the castor bean, which seems capable of sensitizing people having no predisposition to allergy.

Case 7: A. U., 70, married, 42 3rd St., Hospital das Clinicas.

On August 11, patient had his first asthma attack of violent character and was transferred to Sao Paulo. This asthma was not preceded by allergic symptoms. His personal and family allergy history was negative.

Skin tests with 16 inhalants revealed a strong reaction to the castor-bean bran only. The passive transference test was clearly positive.

Comment: This case is similar to No. 6, i.e., a patient without personal or hereditary disposition to allergy had a severe asthmatic attack at the age of 70 years. This demonstrates the extraordinary potency of the castor-bean allergen.

Case 8: R. G. M., 18, single, 1938 Duque de Caxias Ave., Hospital das Clinicas.

Patient had an asthmatic attack for the first time on August 12. This asthma was accompanied by rhinitis and conjunctivitis. He had rhinitis 3 years ago and has a brother who has asthma. Skin tests revealed a strong positive reaction to castor-bean bran only, and the passive transference test was positive.

Comment: Although the patient had rhinitis 3 years ago, he reacted allergically only to castor bean. The other 15 inhalants gave negative results.

Case 9: M. M. N., 17, married, 260 Coronel Lima de Figueiredo St., Hospital das Clinicas.

On August 11, patient had a strong attack of asthma accompanied by conjunctivitis and pruritus of the eyelid. He was transferred to the Hospital das Clinicas in Sao Paulo. Since 5 years of age, he has had allergic asthma and rhinitis, but for the last 2 years has had no asthmatic attacks. His family allergy history was negative.

Comment : The skin tests revealed a strong positive reaction to the castor-bean extract, and a slight reaction to cotton dust. The local passive transference test was clearly positive.

Case 10: J. C., 36, married, 8 P.B.G. St.

For the last 8 years, patient has had bronchitis with violent coughs and paroxysms of dyspnea. One of his brothers suffers from asthma. On August 12, patient had a violent asthma attack and, on August 15, was transferred to the city of Agudos where his condition improved. When he felt better, he returned to Bauru on August 20 and the same evening had a violent attack of asthma. At 2000 hours he was sent again to Agudos, and 1 hour after his arrival he was much better. He then resolved to stay in Agudos.

Skin tests made only with the cotton, cereal, and the castor-bean dust revealed a strong positive reaction to the castor-bean bran and a negative reaction to the other two.

Comment: This case clearly reveals that the source of the allergy was in Bauru and vicinity and that getting away from Bauru was sufficient to free him from asthmatic attacks. The skin tests demonstrated that the allergen was the dust of the castor-bean husk.

Case 11: J. D. P., 9, lives at 1442 Sete de Setembro St.

On August 11, patient had a serious attack of asthma and was transferred to Agudos. On his arrival at Agudos, his asthma disappeared at once. Three days later he returned to Bauru where, after 4 days, he had a violent asthma attack and was sent again to Agudos. Once in Agudos his asthmatic condition disappeared and did not recur during the 15 days he stayed there. He again returned to Bauru and, after 4 days, again had attacks, which convinced his parents to keep him in Agudos. At 6, he had had asthma provoked by the dust of the house, but for the last 2 years he had had no asthmatic symptoms.

Skin tests with the dust of cereals, cotton, and castor bean revealed a strong positive reaction to the latter and a medium reaction to cotton.

Comment: As in Case 10, the asthmatic symptoms started or stopped in accordance with the patient's stay in Bauru or Agudos. The patient demonstrated reaction to the cotton dust and house dust, which confirmed his previous history.

Case 12: M. T. C., 8, lives at 225 San Martin St.

Patient had his first asthma attack on August 11, and, as his condition did not improve, he was transferred to Agudos on August

17. The day of arrival, his asthma disappeared. A few days later he was sent to Bauru, where he had another attack of asthma. He was again sent to Augdos, where he improved. The history of the patient does not reveal personal or family manifestations of allergy.

The skin tests with dusts of cotton, cereals, and castor bean were only positive to castor-bean bran.

Comment: This is identical to the two preceding cases, and the tests were positive for castor bean only.

Case 13: I. M. M., 28, 924 Batista de Carvalho St.

Patient had his first attack of asthma on August 11. Two days later he was transferred to Jaú. He returned to Bauru on September 10 and the next day had a new attack of asthma. He was transferred to Agudos, where the symptoms disappeared. His history revealed that 6 years ago he had had an allergic rhinitis. His family allergy history was negative.

Skin tests done with the dusts of cotton and cereals, and the bran of castor bean revealed positive reaction only to the latter.

Comment: Same as the preceding two cases.

Case 14: N. F., 25, Vila Noroeste.

Patient had her first symptoms of asthma on August 11 and was transferred to Aratibá, where she improved. She returned to Bauru on August 23 and, 2 days later, had a new attack of asthma. She was transferred to Agudos, where the symptoms disappeared. The patient had had an allergic rhinitis 2 years ago and had no history of hereditary allergy.

Skin tests revealed a positive strong reaction to the extract of castor-bean bran.

Comment: Same as Cases 11 and 12.

Case 15: A. S., 38, lives at a ranch 6 miles from Bauru.

Patient had her first asthmatic crisis on August 27. The symptoms described by the patient were not typical of bronchial asthma as they were only lack of air, not accompanied with suffocative breathing, coughs, or rhinitis. She stayed in this state 3 days and, therefore, was transferred to Sao Paulo where she improved but still had some difficulty breathing. Later she stayed a few days in Santos, but her health did not change. She went to Agudos where she still had the same symptoms. Her personal and family allergy history was negative.

The skin tests made with the castor-bean bran and other allergens all proved negative.

Comment: This patient was extremely nervous. Her symptoms were not typical of asthma, and she did not improve completely when she left Bauru, as did the majority of patients with the allergy in question. Probably she was neurasthenic and influenced by the drama of the epidemic as described by radio and newspapers.

Case 16: B. A. P., 20, resides in Agudos.

On August 11, while in Bauru, patient had a violent attack of asthma, which disappeared 3 days after his return to Agudos. In Agudos he still suffered from bronchial asthma, which he had had since he was 3 years old. The cutaneous tests revealed positive reaction to dust, cotton dust, and castor bean. His history revealed eczema and urticaria. His father and two aunts also have bronchial asthma.

Skin tests with cereals, cotton, and castor-bean bran were strongly positive.

Comment: Although this patient left the city of Bauru, he still suffered asthma in a minor degree. A possible explanation is that the patient had chronic asthma and was sensitive to other allergens besides castor bean.

Case 17: E. O., 35, 257 General Marcondes Salgado St.

The patient had bronchial asthma 6 months before his asthmatic attack. After a 30-day absence from Bauru, he returned on September 2 and, the same day, had a severe asthmatic attack that lasted 24 hours. On September 11 he had another attack, which necessitated his transference to Agudos, where he got rid of the symptoms. His personal history of allergy was negative; however, his mother had allergic rhinitis.

Skin tests revealed a strong reaction to the castor-bean bran only.

Comment: The patient evidently was allergic to the dust of castor-bean husk as, on the same day of his return to Bauru, he was attacked by asthma, and had another attack on September 11 in a general repetition of the epidemic.

Case 18: J. R. P., 43, 96 Gerson Franca St.

On August 11, patient had a severe attack of asthma, which necessitated his transference to the Hospital das Clinicas in Sao Paulo, where he stayed 16 days free of all symptoms. On his return to Bauru on September 7, he had another violent attack of asthma: he was tranferred to Agudos where he improved. This patient had bronchial asthma at the age of 18; a brother also has bronchial asthma.

Cutaneous tests revealed strong positive reaction to castor-bean bran and medium reaction to the dust of cotton.

Comment: The patient was free from asthmatic symptoms while in the Hospital das Clinicas; on his return to Bauru, he had another attack of asthma, which led to his transference to Agudos.

Case 19: D. L. S. S., 12, 161 Ezequiel Ramos St., Apt. 5.

On August 12, patient had his first symptoms of asthma. A few days after the attack ended, he went to Agudos, where he was well. On September 5, he returned to Bauru and the same night had a violent attack of asthma. He had to leave Bauru at 0200 hours for Agudos, where the symptoms disappeared. His personal allergy history was negative, but his grandfather had asthma.

Skin tests revealed a strong positive reaction to castor-bean bran only.

Comment: The patient had asthma for the first time during the epidemic in Bauru on August 12 and September 11.

Case 20: E. S., 34, 375 3rd St. in Vila Independencia.

This patient had his first attack of asthma on August 11, and was transferred to Agudos, where he became perfectly well. On his return to Bauru on September 11, he had a severe attack of asthma. Because of this, he moved again to Agudos, where his health improved. His history of personal and family allergies was negative.

Cutaneous tests revealed strong positive reaction to the castor-bean bran extract.

Comment: Same as preceding case.

Case 21: J. W. R., 9, 522 Virgilio Malta St.

On August 11, patient had an attack of asthma for the first time. After 3 days, because of his critical condition, he was transferred to Agudos. In Agudos, the asthmatic symptoms disappeared, and he returned to Bauru, where he again had an attack of asthma. He was transferred to the Hospital das Clinicas in Sao Paulo where he stayed 14 days. Again on his return to Bauru on September 11 he had severe asthma and was taken to Agudos. His history of family allergies was negative.

Skin tests revealed a strong positive reaction to castor-bean bran.

Comment: Same as Case 19.

Case 22: E. R., 54, 1580 Antonio Alves St.

This patient has had asthma for the last 15 years; however, for the 4 months before the epidemic he had no asthmatic symptoms. On August 11, he had a severe attack of asthma lasting 3 days, only improving when he moved to Agudos. He stayed 15 days in Agudos, free of all symptoms, and then returned to Bauru. On September 22, he again had severe asthma, which obliged him to leave at night for Agudos. Once in Agudos, the symptoms disappeared. He later returned to Bauru, again had an attack of asthma and again went to Agudos. His history of personal and family allergies was negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran only.

Comment: Same as Case 19.

Case 23: A. P. M. M., 54, 1381 Gomes Ribeiro Ave.

On August 13, patient had an attack of asthma and was moved to Agudos, where the symptoms disappeared. This patient had had asthma 14 years ago, but his history of personal and family allergies was negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran and a medium reaction to cotton dust.

Comment: Same as Case 18.

Case 24: W. M., 20, 563 Val de Palmas St.

Patient's first attack of asthma was on August 29, when the epidemic was as active among the Bauru inhabitants as it was on August 11. He arrived in Bauru after an absence of 6 months in Penapolis. Upon his return to Penapolis, the asthmatic symptoms disappeared, but not completely. His history of personal and family allergies was negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran only.

Comment: The patient still was not completely cured of his asthma in Penapolis, a city that has big deposits of castor-bean bran, which is used as fertilizer. The patient was a farmer and had direct contact with the allergenic factors.

Case 25: J. A., 39, 570 Antonia Gaugio St.

This patient had asthma when he was 12 and 13 years old. On August 21, in Bauru, he was attacked by asthma with prolonged crisis. On September 12, he went to Piratininga, three kilometers away from Bauru, and there the asthmatic symptoms continued. His personal history of allergies was negative, but his two sons had asthma.

Cutaneous tests revealed a slight positive reaction to cereal dust and negative to castor-bean bran.

Comment: During the epidemic, many patients who were not allergic to castor-bean bran had asthma. On the basis of the symptoms alone, the doctors classified alike all the cases of asthma. This particular case is an example of asthma that was not caused by an allergy.

Case 26: F. M. M., 45, 760 Sete de-Setembro St.

Patient had asthma on August 12 for the first time. Daily crises occurred between 2300 and 2400 hours. During the rainy days he had no symptoms of asthma. The asthma was accompanied by allergic rhinitis. Personal and family history of allergies was negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran.

Comment: Same as Case 19, except that this patient had no asthmatic attacks during rainy days. This could be because the rain clears the dust of mamona and its allergic component from the atmosphere.

Case 27: J. C., 30, 8 P. B. G. Street, No. 547.

For the last 8 years, the patient had had attacks of coughing and breathlessness. On August 12, he had a severe attack of asthma, and, on August 17, he went to Agudos where he immediately improved. On the 20th, he returned to Bauru and the same night had another severe attack of asthma, which obliged him to return to Agudos. His personal history of allergy is negative, but his brother has asthma.

Cutaneous tests revealed a strong positive reaction to castor-bean bran only.

Comment: Same as Case 18.

Case 28: J. R., 3, 722 Sete de Setembro St.

On August 11, patient had a severe attack that necessitated transfer to Agudos, where he spent 20 days in fine health. When he returned to Bauru, he had attacks identical to the first ones. This patient had suffered from asthma attacks since the age of 2. His past history disclosed allergic rhinitis. His father was an asthmatic.

The skin test revealed very positive reaction to castor-bean bran and medium reaction to cotton.

Comment: Same as Case 18.

Case 29: S. V., 32, lives at 102 Sete de Setembro St.

On August 11, he had an extraordinarily severe attack of asthma that necessitated hospitalization. As his condition did not improve, he was transferred to Agudos, where the symptoms disappeared. He had had bronchial asthma for the last 6 years. His personal and hereditary allergy antecedents were negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran only.

Comment: Same as Case 18.

Case 30: D. M. A., 40, resides in Bauru.

On August 11, the patient had asthmatic symptoms for the first time. As he did not improve in Bauru, he moved to Pirajui, where he stayed 15 days free of any asthmatic symptoms. On September 11, he returned to Bauru and had an attack of asthma that lasted 3 days. A few days later, one of the patient's relatives put a bag of castor-bean bran in the patient's bedroom without the patient's knowledge in order to make sure that the castor-bean bran was the cause of his relative's asthma. During the night, the patient had a very severe attack of asthma. The patient's allergy history was negative.

Cutaneous tests revealed a strong positive reaction to castor-bean bran.

Comment: Same as Case 19. Experimental reproduction by the patient's relative gave confirming results.

METHODS AND RESULTS

The investigation of this "allergy epidemic" covered case histories, reactions to skin tests, results of passive transference of antibodies, and the experimental reproduction of symptomatology.

History

The case histories revealed the following:

1. Twelve patients (40%) had asthma prior to the epidemic.
2. Five patients (16.6%) had allergic rhinitis prior to the epidemic.
3. Ten patients (33.3%) had allergic respiratory symptoms for the first time during the epidemic (in August 1952).
4. Ten patients (33.3%) had asthmatic symptoms accompanied or preceded by rhinitis, conjunctivitis, pruritus of the ears, palatitis mouth, and inflammation of nose and eyelids.
5. The majority of patients were free of all symptoms when they were away from Bauru, sometimes only a few kilometers away. For this reason, most of the patients transferred to Agudos, 15 kilometers from Bauru.
6. Symptomatology reappeared when the patients returned to Bauru. Some patients made trial returns four to five times, but each time they had violent attacks of asthma.
7. In the Hospital Santa Casa, symptoms increased or decreased according to the direction of the wind and its intensity.
8. The occurrences of asthma were more numerous in the lower part of the city that formed a small valley.
9. When it rained, asthmatic symptoms decreased or disappeared and no new occurrences of asthma took place.

Agreement of these findings with those from other reports we mentioned previously suggests that the epidemic of asthma was caused by an allergen in the atmosphere of Bauru.

Cutaneous Reactions

The selection of allergen extracts used during the cutaneous tests gave the following results:

1. Verification of pollen concentration in the atmosphere of Bauru City (classical method of Wodehouse): only two pollens were found per cubic centimeter. This was expected, as August is not a plant flowering month.
2. Verification of anemophilic fungi (method of Feinberg) through the exposure of a plate of Sabouraud's agar for 15 minutes. The number of colonies developed was not more than that observed in Sao Paulo by Mendes and Lacaz.
3. Verification of all possibly allergenic materials found in cereal deposits or industrial locations. Bauru has important factories that extract oil from cotton seeds, peanuts, and castor beans. It also has a big railway junction station where a lot of diesel oil is burned.

Sixteen extracts for the cutaneous tests were prepared from the following origins: three fungi (Rhizopus, Hormodendron, and Penicillium); seven principal extracts of cotton seeds and leaves in the factory; three forms of local dust out of the peanut oil factory; dust of the ricinus (castor bean) seed husk, which is known as castor-bean bran; dust of cereals; and a mixture of combustible oils. The extracts were prepared with Coca's solution passed through a Seitz filter and diluted 1:10, 1:100, and 1:1000 in order to be used in skin and intradermal reaction tests. The combustible oils were prepared in a manner identical to known methods used in preparing the extract of a cigarette smoke, i.e., by burning the oil and having its smoke pass through the Coca's solution.

The nine patients in the Hospital das Clinicas were tested with all the extracts, initially with cutaneous reaction tests using 1:10 and 1:100 dilutions and then with intradermal reaction tests with 1:1000 extracts. All nine patients responded with strong positive reactions to the 1:100 extract of the bran of castor-bean husk. Four of these patients (Cases 1, 4, 5, and 9) revealed also positive intradermal reactions of a weak and medium intensity towards extracts of cotton and cereal dust. Those four patients previously had had respiratory allergies (asthma and rhinitis).

The other 19 patients observed in Bauru and Agudos were tested exclusively with cutaneous reaction tests with three extracts: (a) castor bean at 1:100, (b) mixture of cotton dust at 1:10, and (c) mixture of peanut and cereal dusts.

Of these 19 patients, 17 responded with strong and positive reactions to the castor-bean extract; 4 patients (Cases 9, 18, 23, and 25) with chronic asthma responded positively to the extracts of other inhalants. In 2 patients, cutaneous reactions to castor bean were negative: Case 25 had chronic asthma even in other localities, and his condition did not improve after he transferred to another locality 13 kilometers from Bauru; Case 15, as already explained, was an emotionally unstable woman who was unduly impressed by the spread of the epidemic. Her symptoms were merely lack of air, without coughing or other characteristic symptoms of asthma.

Local Passive Transference of Antibodies

In the nine patients interned in the Hospital das Clinicas in Sao Paulo (*Cases 1 through 9*), we effected the passive transference of antibodies by the Prausnitz-Küstner method. The serum of patients was passed through a Seitz filter and injected in doses of 0.05 ml, intradermally, in the back region of two nonallergic patients. Twenty-four hours later they were injected in the same region with 0.03 ml of extract of castor-bean bran at 1:1000, and the test was definitely positive with the nine sera used.

The Experimental Reproduction of Symptomatology

Four patients (Cases 1 through 4) were tested for asthma reproduction by inhalation of the extract of the castor-bean bran. Two of these patients were asthmatic previously; one had an allergic rhinitis, also prior to the epidemic; and one had never suffered asthma or rhinitis until the epidemic. For the test, we used a 1:10 extract, prepared as usual in Coca's solution, dialyzed and filtered, containing 1.2402 of N per milliliter. This extract was first tested for toxic effect, as it had not been treated to extract or inactivate ricin. For this purpose, four guinea pigs were injected, each with 1 milliliter of the extract, intraperitoneally. Earlier, the animals were put in an apparatus to provoke experimental asthma in animals through inhaling 1:10 castor-bean extract for 30 minutes under a pressure of 120 millimeters of Hg from a De Vilbis No. 40 atomizer. The animals resisted the experience.

The same extract was used for the four patients inside a 36-cubic-meter room, well caulked, with an exhauster. Four De Vilbis No. 40 nebulizers were put in the four corners at a height of 2 meters. The nebulizers were connected with rubber tubes to an air vacuum pump. In each nebulizer was put 3 milliliters of 1:10 castor-bean extract. The room was sprayed and kept clouded for 1 hour. Prior to this, the four patients had no asthmatic symptoms whatsoever. To exclude psychic factors, the sick were not informed about the test and were sent to the room on the pretext of an X-ray examination. All emergency precautions were taken, such as having available oxygen, cortisone, adrenalin, and aminophylline.

The results were the following: One minute after their introduction into the room, patient I. B. (Case 1) had ocular and nasal allergic symptoms and, after 2 minutes of stay, had to be taken out because of a typical asthmatic attack. The other three patients, after

3 minutes, started to show the following symptoms: Coughing, wheezing, sneezing, and pruritus. Four to five minutes later, they were removed from the room as they had severe attacks of asthma, which lasted 2 hours. Later, the patients explained that their symptoms were identical to those experienced in Bauru during the epidemic.

Patient A. F. (Case 3) vomited during his asthmatic attack (experimental) exactly as he did during the epidemic.

DISCUSSION

Clinically, there were many arguments in favor of an allergic etiology:

1. Sixty-one-and-a-half percent of patients had allergic respiratory symptoms.
2. Thirty-eight-and-a-half percent of patients manifested, before or during the asthmatic crisis, other allergic symptoms of the nose and the eyes.
3. All 17 patients examined in Agudos were free from the symptoms of asthma soon after their arrival from Bauru. Two patients (Cases 12 and 20) made two or three trial returns to Bauru, but always had asthmatic attacks there.
4. Some patients did not manifest asthmatic symptoms during the rainy days, but did in dry weather. The direction and intensity of the wind were also observed by some clinics with regard to effect on certain patients. These data are important in view of the observation by Grimm(*4*) in Germany that certain areas and localities were affected according to the wind direction.

As for allergic elements, the following aspects should be noted:

1. The high potency of the allergen, described as evident by other authors including Ratner and Gruehl(5) in experiments with animals, could induce an allergic state easily. In fact, 38.5 percent of our patients had never manifested previous allergic respiratory symptoms. We did, however, observe a technician in the oil factory who was not allergic to castor bean with which he dealt for 2 years, yet was allergic to cotton dust.
2. Some patients, on arrival in Bauru, showed symptoms because they were already sensitive. Case 24 is an example; this patient, on his arrival in Bauru after an absence of 6 months, had a severe attack of asthma. This same patient is from Penapolis where he worked with fertilizers made mainly of castor-bean husks. Vaughan(*6*) reported three cases of asthma provoked by castor-bean fertilizers. As for

the patients who continued to have asthmatic attacks outside Bauru, (e.g., Case 16) they probably had chronic asthma and were allergic to other extracts besides castor-bean bran.

3. The allergen is in the husk of the seed and not in the oil; i.e., the harmful agent is the husk dust and the bran, which is used for fertilizers. The oil vapor provokes allergy only when it is contaminated with the dust, as proved by Barnard(*7*). The allergen dissolves in water, precipitates in alcohol, and is not destroyed by heat. Special precautions by the factories against the spread of dust should include collecting the dust in liquids that will contain the allergen.

4. The experimental reproduction of symptomatology is of vital value, as it is not always easy to differentiate between positive skin reactions and clinical sensitivity. Recently (1952), when Small(*8*) studied the allergy of ricinus fertilizers, he said that scientific proof could be obtained; yet he was not enthusiastic about obtaining it as he was dealing with a potent allergen. In Case 30, the patient had a severe attack of asthma when castor powder was put in his bedroom intentionally by a relative. In our cases, we reproduced the symptomatology experimentally and consequently showed the causal relationship between the positive skin reactions and the clinical manifestations of sensitivity. In our method for the reproduction of asthma in human beings, we used normal means of contact without any complications. If that method had failed, we would, of course, have had no choice but to use the direct inhalation method.

5. The fact that the epidemic took place on August 11 is explained by the following: Bauru has had a large castor-oil factory for many years. The process of extracting oil consists in general in squeezing or pressing the castor beans to obtain the oil and bran. At the time of the epidemic, for more profit and better oil production, the factory started a new process of extraction that called for the addition of hexane to the castor-bean paste. After this treatment, the paste was sent to a mill where it was cycloned to dry the castor-bean bran. During the drying, the exhausters filled the surrounding air with clouds of dust, which spread to the nearby localities. Probably the hexane method helped to make the allergen more diffusable under these atmospheric conditions, as the conditions were the same as those caused by a cloud of liquid (inhalants of aerosol).

Although there could be some other explanation, nevertheless, the epidemic started 1 day after the new method for extraction of the castor-bean oil had been put in practice. After the mayor of Bauru ordered the factory to stop using their new method, the epidemic waned. A new epidemic, however, occurred on September 11 and continued until the factory was closed after the population revolted against the castor-bean factory and its method of oil extraction, which had probably not been modified to comply with the sanitary regulations. The patients with chronic asthma continued to suffer, but not as severely as during the epidemic. Other patients who suffered asthma caused by the dust of castor-bean bran really benefited when the factory closed, according to the unanimous opinions of the clinical and sanitary authorities of Bauru.

The prophylaxis for similar occurrences (provoked not only by castor-bean bran, but also by dust of cotton seeds and other substances) should be based mainly on the characteristics of the causative allergen. In the present case, the allergen is soluble in water, resistant to heat, and precipitates in alcohol. Prophylaxis could be accomplished by collecting the dust in water mixed with alcohol in order to dissolve and precipitate the allergen. This liquid should be disposed of in a deep hole, or some similar disposal, for its evaporation could make the atmosphere impure again.

We are convinced that, with the development of our industry, sanitary rules must be more strictly obeyed, not only with regard to castor-bean bran but also with regard to other products such as cotton and linen that cause allergies. Statistics show that people living adjacent to such factories manifest far more allergies than do other people.

RESUME

In August 1952, in the City of Bauru, State of Sao Paulo, the sanitary authorities were notified that within a few days there were 150 cases, with 9 deaths, of an extremely grave bronchial asthma. The allergic study revealed that the cases were bronchial asthma and the other allergic manifestations of the respiratory tract, provoked by allergy to the dust of the castor-bean bran (*Ricinus communis*).

Thirty cases were examined for allergy, and the proof of etiology was evident through history, cutaneous tests, passive antibody transference, and experimental reproduction of symptomatology with four patients.

The epidemic of asthma started with the installation of a new method to extract oil with hexane in a large castor-oil factory in Bauru. On September 11, an epidemic similar to the first one again spread when the factory resumed the same method of oil extraction after 1 month of inactivity. The sanitary authorities ordered the closing of the factory, and thereafter no more asthmatic symptoms of epidemic character were observed.

Suggestions are made for avoiding incidents caused not only by castor-bean bran but also by other strong and potent allergens in factory products.

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MASS ALLERGY CONNECTED WITH THE MANUFACTURE OF CASTOR OIL

By Vilmos Miskolczy

In the summer of 1938, I received an urgent call from a patient. When I arrived, the patient was in the midst of a severe attack of asthma, which I stopped with Astmolysin. In searching for the causative factor, I noted a lime tree in full bloom near the premises and assumed that this tree produced the attack. The attack recurred after an hour and a half and did not entirely cease after the administration of Astmolysin; it returned with its former severity after another 2 hours.

The severity of the asthma and my suspicion directed at the flowering lime tree warranted an immediate change of living quarters, and I, therefore, had the patient transferred to one of the resorts in the Mecsek Mountains. The very same evening, 2 hours later, the patient telephoned me that the attack had ceased completely, his respiration was unimpeded, he had expectorated copiously, and he had no complaints aside from exhaustion. He slept well, and when I saw him the next day, he was completely free from complaints. I was greatly surprised, however, to note that the summer resort was full of huge flowering lime trees. Hence, it was obvious that the asthma had not been precipitated by lime-flower pollen. Thereupon, I visited the patient's home in search of the etiological factor, but could not discover anything suspicious. In my inspection of the court, the apartments facing the court, and the stables, I learned with surprise that there had been other cases of asthma in the building and in the vicinity, which the residents attributed to (that is, rationalized as) colds. In the neighboring houses and, in fact, in the whole street more and more persons were discovered who had occasional and recurring complaints of asthma which, moreover, all seemed to be precipitated at the same time.

From one of our giant oil factories on this street, I learned that a few days before they had been manufacturing castor oil. I requested a sample of ground castor seeds so that I might ascertain whether this ricinus grit was capable of producing asthma. The central directorate of the factory authorized me to receive a quarter of a kilo of grit. Since I was urgently needed elsewhere, I just opened the package, looked at the grit, smelled it, repacked it, and put it aside. After a few minutes I began to sneeze, perhaps as many as a hundred times in a few minutes, then after the sneezing had stopped, I developed a burning sensation in one of my eyes, which was followed by itching; but after about 2 hours this, too, stopped. Toward evening, 5½ hours later, I began having breathing difficulties, which developed into a typical asthma, and the attack ceased only after about an hour and a half, without any medication, leaving me in an exhausted state. I had not had such attacks before, nor did the attacks recur afterwards. I was forced to the conclusion that ricinus grit is indeed capable of causing attacks of asthma.

Before proceeding to the description of the pathology and therapy of the cases that I observed, I would like to say a few words about ricinus itself, its industrial processing, and the hygienic aspects of the plant.

Ricinus grit is the ground seed of *Ricinus communis L.* According to Hager(*1*) the seed consists of 24 percent husk and 76 percent kernel. The kernel contains 45 to 50 percent oil. The seed is first husked, then the kernel is ground. It is this ground substance that is subsequently utilized industrially. The oil is obtained either by extraction or by pressing. The extraction is carried out mainly with petroleum ether, in which case the castor oil (oleum ricini, oleum palmae christi, oleum castoris) remains in the grit only in traces. The second process, according to Bernatzik-Volz(*2*), is to press out the seed between hot iron plates under great pressure. The pressing can also be performed with cold plates. Some plants first use cold pressing; the oil obtained in this manner has a mild laxative action compared with the oil obtained by the hot process, in which the laxative action is drastic. Likewise, the oil obtained by extraction also has a drastic laxative effect, especially if the extraction is carried out with ether or absolute alcohol(*2*), presumably because these methods enable substances of drastic laxative effect to get into the oil in larger or smaller quantities. According to Lajos David(*3*) the drastic effect of freshly pressed oil may be reduced by repeated washing with hot water or boiling with water, which causes the proteins present in the castor oil to be precipitated. The water is subsequently eliminated by heating. The cake remaining after pressing contains 7 percent residual oil. During pressing, the toxic albuminoids present in the seed do not go into the oil, but remain in the press cake. One such toxic substance is ricin(*4*), which is present in the kernel in the embryo and the endosperm(*2*). According to H. Stillman, ricin is a protein that causes severe inflammation, swelling, bleeding, and intoxication of the gastro-intestinal mucosa. In 1897, Elfstreud(*4*) noted the inflammatory and necrotizing effect of ricin.

Mayer and Gottlieb(*4*) list ricin among the chemical substances causing inflammation. This list of inflammatory substances includes those that produce neither tissue rupture nor necrosis but only alter the permeability of the arteries, dilating them and rendering them increasingly permeable. These are the specific arterial poisons that, according to these authors, produce similar changes in the lymphatic vessels. This group includes protenoid toxins, such as tuberculin, diphtheria toxin, abrin prepared from the seeds of *Abrus precatorius*(*5*), ricin, the toxin of pollens, hay-fever poison present in the pollen of flowering grasses, a few snake poisons, bee poison, Kalahari arrow poison, and substances present in berries and lobsters that can produce urticaria the same way as a subcutaneous injection of histamine. In more sensitive individuals these agents cause strong hyperemia and an intensive serous impregnation of the tissues.

When placed on the skin, these substances, provided they are capable of being absorbed by the skin, cause larger or smaller blisters filled with serum containing abundant amounts of red and white blood cells. These specific arterial poisons, however, do not cause such symptoms in every person or, in a wider sense, in every animal species.

Thus, according to Mayer and Gottlieb(4), ricin, abrin, snake poison, and Rhus toxicodendron have no effect on cold-blooded animals but, on the other hand, exert a strong action on humans. Snake poison is absorbed only through damaged skin, but ricin and abrin are able to exert their effect through undamaged skin also.

The nature of the reaction to these agents depends on the subject's disposition, which may be positive or negative in the sense of a specific sensitivity or an aspecific insensitivity. This disposition is present in some individuals to a greater extent than in others. The disposition may change under the influence of external or internal factors. The irregularly reacting organisms, that is, the allergic organism, or the organism reacting differently, changes its reactivity after the infection or after an injection of an antigen-forming character(6). This reactivity, however, may also change under the influence of absorbable substances that enter the organism by other routes, such as by way of inhalation or through the gastro-intestinal tract.

This tendency to react differently may be acquired from or be caused by the effect of the albumin toxins that enter the organism by the above-mentioned routes (anaphylaxia) — or it may be congenital (idiosyncrasy). Anaphylaxia occurring in furriers and garment workers is well known. Similar phenomena are frequently observed in children after the consumption of eggs and dairy products(7), and in adults who approach heaps of manure, stables, and flowers. Sensitized persons (anaphylaxia and idiosyncrasy) react with hay fever, or hay asthma, to pollens during the period of first flowering of grasses in May and June and the second flowering in September. Ortner(7) attributes this phenomenon to the disintegration of cells produced by the effects of proteins foreign to the species. According to Ortner, this is the explanation of the development of asthma after x-ray irradiation or, in the case of leukemia, after treatment with vaccines. This, too, is the explanation of the asthmatic attacks occurring in the case of anemia hemolytica, as well as after tuberculin injections, and on treatment with certain drugs (aspirin, phenacetin).

Ricin, which is capable of acting in the same manner, is found in the castor seed. According to Hager(8), the ingestion of 1 to 2 grains leads to severe diarrhea and vomiting; nevertheless, the 1887 edition of this work(8) still recommended the use of castor seeds as a laxative. According to his prescription, one should take, in the morning, 1 to 2 spoonfuls of a preparation made up of 10 grams seed, 5 grams gum arabic, 10 grams water and 75 grams sirup. According to Bernatzik-Vogl, a girl in England had died after ingestion of 20 seeds, and dogs, after ingestion of 12 seeds. Cows are fatally poisoned on ingestion of the pressed cake, which is used for the extermination of field mice and rats. Whether the persons in contact with the pressed cake developed allergies is not treated in the reports; any symptoms that may have been observed are ascribed to other causes.

After this introduction, I would like to report on my case material. I observed a total of 45 cases connected with ricinus manufacture; they may be classified as follows:

11 cases of asthma;
27 cases of urticaria with very severe blister formation;
3 cases of conjunctivitis without other symptoms;
2 cases of severe bronchitis;
2 cases of marked swelling of the joints.

Of the 11 asthmatic cases, 8 were women and 3, men. The women were more seriously ill; some among them were forced to move into other, less comfortable or pleasant apartments in another part of the city. Family members of these patients were not sensitive to ricinus. Among the male patients were two officials of the Hungarian State Railroads, who would come down with attacks of asthma every time they were required to handle sacks of pressed grit. Often they would be reminded of the nature of the article being shipped only through experiencing a difficulty in breathing.

The onset of the asthmatic attacks coincided with the start of ricinus processing at the plant or the time when the grit was being filled into sacks or shipped. Persons not connected with the plant were never aware of the fact that castor-oil processing was going on; for years they had attributed their choking sensations to colds.

Among the factory workers, too, were many who, in the course of their work with castor seeds, came down with attacks of asthma, urticaria, conjunctivitis, or bronchitis; these workers sooner or later left their jobs, saying they could not tolerate working with these dusty materials. After the causative factor had been identified, many residents moved to other parts of the city in the interest of their ill relatives. After the population at large became aware of the problem of ricinus processing, which I brought to their attention, the commanding officers of the military barracks located nearby petitioned the municipal authorities to forbid manufacture of castor oil, since there had been many cases of illness among the personnel from unknown causes. Thus, with my own 45 cases, the total number was in excess of 100.

In the past I had used only Astmolysin to halt asthma attacks. In the majority of cases one injection was sufficient; a second injection was only rarely necessary. In only one case did the attack recur after a period of one-half to one hour, and it ceased only after a change of environment. More recently I have been prescribing Antistin tablets, one or two according to the severity of the complaint, administered in one dose or at half-hour intervals. So far Antistin has halted the attack in every case, even when the attack was fully developed. In one case when the attack was particularly severe, (led by my desire to halt the attack as quickly as possible) I again turned to Astmolysin in order to shorten the avoidable 12- to 30-minute delay necessary for the development of the action of Antistin.

It might be of interest if I described my prophylactic treatment of a patient who reacted to ricinus with an asthmatic attack.

The patient had been forced to move away from the vicinity of the factory because he suffered attack after attack during the period of manufacture and shipment. He was given three Antistin tablets daily for the first week, one tablet daily during the next 2 weeks, then one tablet every other day for the next 3 weeks. On the eighth day after starting with the tablets, he returned to his former apartment (at a time when ricinus processing was going on at the plant), but did not suffer any attack or experience any difficulty in breathing. During the period he was taking the tablets, he would spend 1 to 2 hours in the neighborhood without any complaints. Nor was there any reaction when, after having discontinued medication, he would visit the area for an hour or two. At the present time, 4 months after he took the last tablet, he is able to spend hours in the neighborhood of the plant without any complaints. Although one cannot derive any conclusions from this isolated case, it nevertheless seems to point to the fact that Antistin is suitable for bringing about desensitization.

The skin symptoms observed in the 27 cases began, without exception, with an itching, tickling sensation on the neck, on the back of the hand and on the forehead. The itching changed into a mild, then more and more intense burning sensation at the same time the skin became red with the formation of lens-shaped blisters about the size of a two-forint piece, which began to swell and in certain cases attained a thickness of about 1 inch. Under these conditions, the movements of the neck were restricted because of tension. The patients complained of sensations of creeping ants, experienced first at one point, then another. In 25 of the 27 cases there was monolateral or bilateral conjunctivitis (more frequently only monolateral). The conjunctiva became inflamed within seconds, with the development of a strong stinging, burning sensation in the eyes; the vision became blurred partly from the strong lacrimation and partly, perhaps, from the swelling of the cornea. The patients suffered such pains and the irritation caused by light was so strong that they were forced to keep their eyes closed.

In most cases I saw the patient one-half to two-and-a-half hours after the onset of symptoms. The injection of calcium administered intravenously and the use of a cool compress brought relief only after several hours, and sometimes the patient had some complaints even after 3 days. More recently, one-half to two-and-a-half hours after the onset of symptoms, I gave the patients two tablets of Antistin, which halted the symptoms within a half hour. The patients became free of complaints. In a few cases, however, when a patient who otherwise had no more complaints would absent-mindedly rub his previously urticarial skin within a period of 24 hours after the onset of symptoms, he would experience a burning, itching sensation, which, however, would disappear after a few minutes. In one case, after the skin symptoms had been alleviated, I had the patient take a thorough bath. After the bath no itching developed, even when he rubbed his skin, which I explain by the fact that although the ricinus dust deposited on the skin would have led to further urticarial symptoms when rubbed into the skin, the Antistin already acting in the organism prevented the development of such a relapse.

In three cases, the sole symptom was conjunctivitis developed under similar circumstances and having a similar course.

In two cases, I observed bronchitis; one of these cases was a year-and-a-half-old infant whose bronchitis could not be brought under control despite a wide variety of treatments. When the family moved to another part of the city the patient improved; eventually, the bronchitis ceased entirely, to recur only when the plant was engaged in ricinus manufacture. The distance between the new apartment and the factory is about 1 kilometer, and the factory is located east of the apartment; the predominant wind direction in the city is east-west, west-east.

The two cases of swelling of the joints involved the knee, wrist, and ankle joints. In one case, the finger joints also were swollen. Calcium injections administered intravenously and compresses brought improvement only after 12 to 24 hours. After taking two tablets of Antistin, the patients felt better after a half hour and were completely well after an hour.

It is interesting that the same individual always reacted to castor seeds with the same symptoms. I did not observe any variation in the symptoms. The patient who exhibited asthma the first time again had asthma the second and third time. The same held true for urticaria, conjunctivitis, bronchitis, and swelling of the joints.

Thus we have seen that many persons living in the area, factory workers or individuals coming in contact with the grit of castor seeds away from the plant, fell ill with allergic symptoms. Let us examine the stages in which contact with the allergen is possible. For this we need to describe briefly the steps used in ricinus processing. Whether the manufacture of the oil is carried on by pressing or extraction, the preparatory treatment is identical. The castor seeds are husked between rubber cylinders; the light husks are blown into a collecting chamber by an air current, and the heavy seeds are carried to the sieve.

Husking causes a great deal of dust. The workers, in an attempt to overcome the irritating effect of this dust, open the windows of the premises, and the dust enters the atmosphere unimpeded. In the course of husking, many seeds are damaged, and some of the resulting dust also enters the atmosphere; however, because of its high oil content, the volatility of this dust is somewhat lower. This is the first stage of the harmful effect of castor dust. It can be eliminated only if the workers perform this phase of the processing with all windows closed, wear dust masks, and employ a fan that exhausts into a water tank. The workers shoveling the husks or the husk powder into the furnace should also wear dust masks. In the course of burning the husks, if the draft of the furnace is too strong, much unburned dust may enter the atmosphere, thus causing additional cases of illness.

The seed deprived of its husk is ground. This is the second stage of the harmful effect of castor dust. Although the grit is rich in oil and hence not readily carried into the air, the grinding and the emptying of the grinder should still be carried on in a closed system.

From this point on the procedure is different, depending on whether the seed is pressed or extracted. In the case of extraction, the grit is covered with petroleum ether and agitated in a closed drum for six hours, during which time the oil is fully extracted. The petroleum-ether solution is then decanted and the dry grit, which is practically free of oil and relatively light, is taken from the drum. This is the third stage of the harmful effect of ricinus. The light dust quickly enters the atmosphere. This part of the work cycle should only be permitted by workers wearing dust masks, and the grit should be poured into densely woven sacks, or better, paper bags.

The sacks are taken to the warehouse and then shipped; the latter operation is the fourth stage of the harmful effect of ricinus, since in the course of loading and unloading the trucks or freight cars, much dust enters the atmosphere from the coarsely woven sacks.

In the case of pressing, whether by an Elbex or other type press, the residual grit contains about 8 percent oil, making the grit heavier and more sticky; although the dust in this case is less volatile, a considerable amount nevertheless enters the air even under these circumstances. Hence the shipping of ricinus grit, unless it be in the form of briquets, should be permitted only in densely woven sacks or in paper bags.

Finally, we must discuss the end use of ricinus grit.

According to H. Ost, the lipase present in castor seeds exerts a hydrolyzing effect on fats. When 100 parts liquid fat is treated with 5 to 10 parts ground ricinus seed and the mixture, together with 60 parts water and a little acetic acid and manganese sulfate as activator, is kept for 24 hours at 25°C, between 80 and 85 percent of the fat will be saponified. This byproduct of ricinus grit is dericinated by means of a special process and is used as fodder. According to other information, the ground seeds are used abroad as fertilizer, which use provides ample opportunity for the development of illness.

For the past several weeks, experiments have been carried out in Hungary to determine whether the approximately 2,000 wagons of ricinus grit now in storage could be used as a binding agent in coal-briquet manufacture. The results of these experiments are not yet known, but if they are positive, it will be necessary for physicians, both within and outside the plants, to watch for any unexpected outbreaks of asthma, urticaria, bronchitis, and other allergic illness in view of the fact that through the dust of the coal briquets tens or hundreds of thousands of persons who heretofore have had no contact with ricinus will be exposed to this agent; the attending physician must, therefore, keep in mind the possibility that in these cases ricinus dust may be the causative factor.

SUMMARY

The author describes 45 cases of allergic illness precipitated by ricinus grit: 11 cases of asthma, 27 cases of urticaria, 3 cases of conjunctivitis, 2 cases of bronchitis, and 2 cases of swelling of the joints.

All these cases occurred in the vicinity of the oil factory and always during the period when castor seeds were being processed. The calcium injections formerly administered led only to slow and delayed improvement; satisfactory results were obtained only with Antistin tablets, which stopped the asthma attack in a half hour and acted with similar effectiveness in the case of urticaria, bronchitis, and swelling. A patient with proven allergy was given prophylactic doses of Antistin with the result that he was able to return to the infected area and maintain his desensitization even after the medication had been discontinued.

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ALLERGIC MANIFESTATIONS DURING PROCESSING OF CASTOR BEANS

By Karel Rejsek

New industrial raw materials frequently bring about new problems in occupational medicine, problems that might have been anticipated but that were not known until this time as questions in industrial toxicology. This is what took place in connection with our first industrial processing of castor oil beans, a process that was started by us for the first time in the middle of the year 1947. Almost immediately there appeared occupational diseases, and rather severe ones at that. Since we were taking care of the establishment, both as regards its occupational health hazards and the medical problems of its personnel, we were able to follow the course of the whole problem from the very beginning to the end, insofar as it can be said that the problem no longer occurs. Our technical and medical intervention effectively neutralized the deleterious health factors in the plant in this respect, although we dare not say with full assurance that they have been completely eliminated.

Technical Employment of Castor Oil and Its Properties

Formerly castor oil was utilized merely as a medicinal preparation and, in some instances because of its special properties, as a lubricant in engines revolving at high speeds. During the last war, because of the shortage of linseed oil, in Germany and in America there was a search for a substitute oil. Experiments showed that the transfer of a double bond in the ricinoleic acid of castor oil produces a similar and in some respects a superior oil to linseed oil. This was why in our country also, because of the shortage of flax seed, we imported large quantities of castor seeds from South America.

Description of the Factory

The castor beans are received in jute sacks and are unloaded from the railroad freight car onto an electric powered dolly wagon to be transported to the cellar warehouse. Here, the jute sacks are cut through and their contents poured into the opening of the chute. This is accompanied by some dust, primarily from the jute sacks; the surrounding air is permeated with a heavy odor, reminiscent of the smell of poppy seed. From the warehouse, the beans are automatically transported to the storage room floor, where they are piled in large heaps. Here, a few workers handle the beans with shovels, pushing them toward the opening through which they are conveyed by a moving spiral device to the grinder. The resulting grind in measured lots is then milled in a rolling mill where the first oil is obtained. The groats after this processing are pressed into flat cakes that are then again fed into a hydraulic press battery. Here, the material is pressed under very high pressure to obtain the last remnants of oil. The compressed flat cakes, the size of a doormat, are then loaded onto moving belts and conveyed to storage. They have a sharp, coarse surface that causes surface wounds easily. From the mill and from the press, the oil flows to the vats below, where it is left to stand. On its surface there soon forms a volatile fermenting slime, which is collected and discarded. The oil is refined with steam and hydrochloric acid and purified in filtering presses. It is exposed to sulphuric acid to effect the shift of the double bond.

It is worthwhile to emphasize that, principally during the course of pressing in the hydraulic press, thin sprays of oil from flat cakes of the raw product are constantly showering the air around the press, and the atmosphere around the mill and especially around the press is saturated with a heavy odor. Everything one touches feels oily, and the clothing of the workers in the press area is thoroughly soaked.

The pressed material still contains approximately 8 to 10 percent of oil, which cannot be obtained mechanically by pressing but can be extracted. This is done in another plant. The mats of raw material are loaded and carted away, often somewhat rotting. The mats are brittle and break easily; considerable amounts of dust are formed and carried by the wind currents from the area far into the surroundings. In the other plant, the mats are ground and conveyed by means of a screw spiral conveyor to the extraction chambers. When a chamber is full, it is closed hermetically and filled with benzine heated to 300°C. The benzine is permitted to act for a certain period on the material and then is released to the evaporation vats. After the chambers are opened, the extracted material is raked to a wagon and transported to a storage place where it is mixed with phosphate fertilizers. The resulting mixture is eventually used for fertilizing the fields. The castor bean matter cannot be used as fodder because it still contains ricin and ricinine, which are very toxic substances as we shall discuss later.

The mixture of benzine and oil in the evaporation kettle is processed by steam; the benzine is distilled off leaving the raw oil, which is refined by the constant process and then rectified as described above. The extraction process is quite faultless; at no time during my inspection was there the slightest scent of benzine, not even when, after release of the material, I crept halfway into the extraction chamber. At the present time, the process has been simplified. After the grinding of the beans in the mill, the groats are extracted directly in the chambers.

Clinical Observations

As described above, there is a great amount of dust generated during the cutting of the sacks containing the castor beans, and the air is filled with an intoxicating smell. We saw in two workers after no more than 2 hours of work a severe conjunctivitis with chemosis, the conjunctiva, swollen and projecting beyond the lids, secreting large quantities of sticky secretion to make the eyes and lids adherent as in sleep. We have the impression there is an interplay here of three factors: mechanical irritation from the dust from the beans and possibly from the jute sacks; irritation from pathogenic microbes, although we must stress that we were unsuccessful in culturing any of the latter from the beans; and finally, irritation from the volatile oils. The conjunctival inflammation precedes later disease processes, specifically an exclusively allergic, extremely severe asthmatic bronchitis, which is described below.

It is further necessary to discuss the skin affections that underlie and accompany the other processes. Below are two clinical case histories, one of a patient with acute pruritic eczema and the second of a patient with acute dermatitis.

S. J., c. h. 8314/47, worker, age 44, was stationed on the loading floor from which he shoveled the beans toward the opening leading to the rolls where the beans were to be ground. He had never had any kind of eruptions or any predisposition to allergic manifestations. After 14 days of work, he had an itchy and burning eruption on the exposed surfaces of the upper extremities.

Objective findings included an exanthema composed of papules, pinhead-sized, quite red and delicately excoriated on top, extending over both forearms, especially on flexor surfaces, and around the elbow joint. The papules were surrounded by an inflamed border. In spots the papules had a brownish red color (Konopik).

The patient's bodily appearance was athletic; he was hypertensive with BP 225/150 millimeters mercury, with opalescence of albumin in the urine. Hemogram revealed eosiniphilia, 7 percent; absolute number of eosinophils, 750 eosinophils per cubic millimeter. Skin test with the allergen was negative.

We were thus dealing with acute pruritic eczema.

The second type of disease usually appeared in all of the workers who worked in the press area with the raw material of processed castor beans. It always started with fine wounds of the skin.

J. K., c.h. 8312/47, on the second day after he began working with the castor beans, had already wounded himself in a few places with the sharp edges of the material. The wound immediately had an angry red color, burned constantly, and became surrounded by an eruption that spread into the surrounding skin and burned to the point that he could not sleep. It always improved on Sunday. He had never had eruptions prior to this time, nor did he have any history indicating predisposition to any allergic manifestations.

Physical examination revealed that both of his forearms, mainly on the flexor surfaces, were covered by a rash with numerous excoriations surrounded with a sharp red inflammatory border. In spots there were small papules topped with tiny areas of clotted blood. The anterior surface of the thighs and the chest had small erythematous areas, dark red, having no sharp borders (Konopik).

The patient was a man of slender build, with eosinophilia of 7 percent, absolute 434. His intradermal test with the castor allergen was positive down to a dilution of 1:100,000.

The most troublesome, however, was a third type of affection; i.e., the respiratory system disease appearing as bronchitis with asthmatic attacks. This malady appeared not only in those workers directly in contact with the castor material, but also in office workers whose contact with this substance was extremely rare or absent altogether; e.g., those merely near the office windows that opened toward the court where the material was unloaded.

S. V., c.h. 8306/47, clerk, age 57, had his first symptoms a few days after castor beans began to be ground in the plant. His eyes began to burn and were inflamed; gradually his breathing became more labored day after day; and within about 14 days he began to have severe attacks of dyspnea with painful coughing. When he was absent on sick leave, the difficulties ceased rapidly, to resume in full swing as soon as he returned to the plant.

Objective findings included generalized sibilant rales in this leptosomatic man, BP 115/70 millimeters mercury. The intradermal test was positive even at a dilution of 1 in 10 million. Hemogram showed eosinophilia of 20 percent, absolute 840.

The allergen was prepared from defatted groats of the bean. Oils were removed by soaking the material for 24 hours in tetrachloromethane. The extract was prepared according to the Evans phosphate process (Liska).

The allergic state of hypersensitivity was present in varying degrees in the other patients. In one patient an injection of 0.1 cubic centimeter of the antigen diluted to 1 part of 10 million was followed by an immediate severe edema of the whole arm. Hemograms consistently revealed eosinophilia, the highest being 22 percent with absolute number of 2838 eosinophils per cubic millimeter in that particular case. The clinical symptoms in a few instances included sudden urinary and fecal urgency at the beginning of the attack. Pulmonary auscultation findings were mostly of dry phenomena with no other positive findings in the lungs.

Processing of the dry material in the other plant was accompanied by a complex of signs that were slightly different from those just described. Immediately upon the start of work with the castor material respiratory difficulties appeared, but these did not persist when direct contact with the substance continued; however, typical asthmatic attacks during the night were usual.

J. P., c.h. 8533/47, had had acute rheumatism 10 years earlier, but was otherwise always well. When the first groats were delivered, he tasted them as he had been used to doing with poppy seed and other similar material. Soon thereafter he had a severe attack, which lasted for nearly a week. About 14 days after returning to work, he reported that he had difficulty breathing during the day and that his eyes were burning and full of tears. At night he experienced sudden attacks of dyspnea, which awakened him. These attacks recurred regularly every night at about 10 o'clock, midnight, and at 4 in the morning. Each attack lasted about 10 minutes; he could not expectorate and became all soaked with sweat. He had an athletic build, was well nourished, and had lungs quite normal. The intradermal test was positive; hemogram showed eosinophilia of 7 percent, absolute 728 eosinophils per cubic millimeter.

In all, we investigated 28 patients, 15 of whom had typical dyspnea attacks. According to a communication from the plant management, four additional employees suffered dyspnea attacks while working with castor beans. Not including those with skin symptoms only, more than one-half of the total staff became ill.

Industrial and Personal Protective Measures

One of the first industrial protective measures we recommended was the thorough enclosure of the press to prevent spraying of oil into the atmosphere, and also analogous steps to eliminate, as much as possible, the dust in the air. The radical acceleration of the whole process, as mentioned before, was one of the most effective steps taken.

From the medical standpoint, there were again three problems. We recommended that workers wear adherent eye-goggles to prevent inflammation of the conjunctiva, especially during the process of unloading the castor beans. With regard to skin diseases, we recommended the most attentive care of each small wound. Since skin affections appeared primarily on the exposed areas, we recommended the use of thinly knitted yarn gloves and clothing so as to prevent traumatization of the skin (Konopik). We excluded from work with castor beans those employees having any history of urticaria or eczema. The glove and clothing prophylaxis was carried out consistently only in two employees; in these it fully substantiated its value. After the change in the manufacturing process, these precautionary measures were no longer necessary as the skin affections soon ceased in a spontaneous manner.

The problem of preventing diseases of the bronchitis type and the manifestations of dyspnea was more involved, especially during the early period when the detailed mechanism of pathogenesis was not at all clear. For this reason, we began by issuing directives to the plant physicians to ensure careful selection of workers henceforth.

It was necessary to exclude from this work or to prevent the hiring of any individuals who were in any manner sensitized because such persons invariably reacted with severe symptoms. Thus, the patient V. K., c.h. 8313/47, reported during the clinical examination that he had worked during the war as a milker of cattle and that he had mild dyspnea as soon as he came close to the stables. Over the course of time the symptoms became worse, and eventually he had to stop this kind of work altogether. But some dyspneic symptoms remained. As soon as he started to work with castor beans, severe dyspnea recurred, and asthmatic attacks worsened so rapidly that he had to be hospitalized.

The man had an athletic body build. Pulmonary auscultation revealed hypersonorous sounds down to TH_{12}; breathing was difficult and accompanied by rales. Intradermal test was positive even at a dilution of 1:100,000.

We recommended excluding from work with castor-bean material all persons in whose history there were convulsions, exudative diatheses, urticaria, hay fever, and asthma bronchiale and even those whose parents, grandparents, or other close blood relatives had such diseases. We also recommended excluding from this occupation employees with a history of Quincke's edema, as well as those who had had acute polyarthritis (our previously mentioned case K. J., c.h. 8526/47, is an example of such a case); also to be excluded were those with migraine types of headache (Z. Fr., c.h. 8530/47,) and chronic colitis (B. Fr., c.h. 8309/47).

Therapy of the Asthmatic Manifestations

We had the problems of both therapy and prophylaxis against new attacks in persons who did not have any allergic predisposition as evident from their clinical history. Immediate intervention was essential because workers were abandoning their work. Although we were well aware of the nil or poor results obtained in the therapy of bronchial asthma with antihistamines, we nevertheless tried this type of medication. To our astonishment and delight, the treatment gave excellent results in all cases except one. In that one case, the asthmatic attacks, which were occurring every night, actually ceased immediately after antihistamines were prescribed; coincidental diarrhea ceased; and the patient began to regain weight. The improvement, however, was only temporary. After only 1 month, nightly attacks of asthma recurred, and they continue to persist to this day although the patient no longer has any contact with castor beans. Perhaps the following detail is irrelevant, but it seems worth mentioning that the patient showed no eosinophilia (relative, 5 percent; absolute, 330).

The antihistamines were effective prophylactically also. Two employees, after the very first attack, were given antihistamines, and further attacks of asthma did not appear although both continued to work continuously with castor beans. After this success, we routinely gave Antistine to all as a preventive, and new attacks of asthma did not reappear in any of the patients so treated. We are reluctant to claim that this is the complete solution as future experiences must indicate the degree to which antihistamines can ensure permanent success.

To test the properties of the substances obtained from defatted materials, we experimented with the allergy-inducing tendency of the non-fat part of the bean, a substantial proportion of which is proteinaceous matter. Osborne, Mendel, and Harris isolated from this part a very toxic albumin that they named ricin, another globulin compound, and finally a substance of alkaloidal nature, ricinine. We prepared both of the protein fractions by extraction with salt solution, dialysis, precipitation with ammonium sulfate, another dialysis, and finally distillation in vacuo according to the method of Merck.

We tested both of the fractions, the globulin and albumin, for their content in free histamine-like substances. With all precautions we carried out preliminary tests on the distal guinea pig ileum. The albumin fraction had no effect on the intestine; the globulin fraction, however, elicited a potent contraction, even at a very dilute concentration. The toxicity was tested in mice, and the separate albumin fraction was about 10 times more toxic than the globulin one. Our clinical observations indicated that the allergen is thermostable. We saw a case of asthma in a worker who worked only with the groats, which are extracted after 2 hours of soaking in benzine at 300°C.

The above finding of histamine clarifies at the same time both the skin manifestations of allergy and the good effect of antihistamines. The good effect in general with asthmatic patients and the benign course is explained by us as being attributable to the fact that we are dealing here with monovalent hypersensitivity, in other words, primary asthma.

Discussion of Findings and Review of Literature

The literature pertaining to the action of castor oil and especially to the toxic effects of castor beans is very abundant, although most of the studies were done toward the end of the past century and the beginning of the present. Allergic manifestations, however, are mentioned only in individual instances. Thus, Borchardt in his 1913 study about the effects of pituitary extract mentioned that he was seized by attacks of asthma himself whenever he was preparing a castor-bean extract. Pituglandol was successfully used by him to terminate the attack. Jacoby, in his publication about ricin, abrin, and crotin in Hefter's Experimental Pharmacology, says that he had a servant who had helped Ehrlich in his first experiments with the castor bean 25 years earlier. A few particles of castor-bean dust placed on his nasal mucosa was sufficient to evoke a typical asthmatic attack. In 1928, Figley and Elrod described an epidemic of bronchial asthma in Toledo; not in the plant that manufactured castor oil, but among the people that lived to one side of the plant. Whenever the wind blew from the direction of the castor-bean milling area, the affected people suffered attacks of asthma. They studied 30 of the patients, all of whom showed positive tests to castor dust. In Germany during the last war, Stienen described a disease endemic in workers in a castor-bean mill, where tests were also positive. In more recent times in Belgium, De Laet described an occupational affection of the skin of a type similar to that which we, ourselves, saw. In 1948, Woringer described three cases of castor-bean allergy with skin manifestations, conjunctivitis, and rhinitis.

Finally, we wish to acknowledge the assistance of Dr. Konopik in the study of the skin affections and that of Docent Rasek in our experimental studies done under his direction.

SUMMARY

During the pressing and extraction of castor oil from castor beans and their groats, workers became ill with manifestations of allergy. They experienced severe conjunctivitis, acute dermatitis, and eczema as well as attacks of asthmatic breathing. The attacks came within the first hours of work with the material, upon which the employees were dismissed immediately from the task, or the attacks began after considerable work with the material from castor beans with breathing becoming more and more labored culminating eventually in typical asthmatic attacks. Finally, a third type of affection took place during the rest periods away from work and was characterized by nocturnal attacks recurring at certain regular hours. In all instances, a significant degree of eosinophilia and a positive test to the phosphate extract obtained from defatted castor-bean groats were found. Antihistamines were valuable, both therapeutically and prophylactically. This unusual success we attribute to the fact that we were dealing with a monovalent hypersensitivity, i.e., primary asthma. Results of the experimental studies make this explanation likely. In the oil-less part of the bean there are proteinaceous substances. By ammonium sulfate salting and dialysis, we separated the albumin and globulin components. The globul fraction contains free histamine, as we determined by tests on guinea pig ileum.

ADDENDUM

Inasmuch as a period of about 10 months elapsed between writing this article and receiving the proofs, we have some further observations to add.

Castor-bean pressing in the manufacture of oil was suspended for about a half year and then again instituted for about 2 months with the processing of a new batch. The new operation brought about a repetition of both the skin and bronchial allergic symptoms. Antihistamines were effective only in typical asthmatic attacks; in skin affections and in asthma accompanied with nocturnal attacks of coughing, they failed completely.

In another plant, a further treatment of the groats was begun in order to obtain casein, which is used in the manufacture of glue.

In spite of the fact that, from the very beginning, the work was done under very poor hygienic conditions, no allergic diseases were observed in this instance. In some instances, the employees (9) reported mild difficulties consisting of lightly irritative nocturnal coughing. In not a single one of these cases was the test with the castor allergen found positive. After installation of exhaust ventilation, the difficulties ceased. The extracted groats and the final product, containing about 50 percent casein, contain only traces of histamine.

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ALLERGY TO RICINUS

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Actually, this paper should have been entitled "Ricinus Asthma," because fundamentally it is to this problem that we wish to devote our communication. The broader term is nevertheless retained considering that the castor bean, as an allergen, can cause not only respiratory ailments but also pathologies involving other organs; in particular, shock states with very severe enterorrhagia (as described by Roy A. Ouer) and cutaneous reactions that at times—as one of us has observed—may be associated with changes occurring in the respiratory system.

In speaking of allergy, we wish to emphasize that we are using the term in its strictly orthodox meaning as adopted by the majority of authors; that is, a process of sensitization and precipitation of attacks. By ricinus asthma, we mean those pathological manifestations that are definitely due to a sensitization by the ricinus antigen and occur only on contact with this antigen.

Of the various angles from which this problem has been studied so far, not a single one permits a study of a general and fundamental character, focused on the increase in the number of asthma cases, that would draw the interest to the etiological factors provoking this disease and the causes responsible for the increase.

That the rate of allergic illnesses in general and of asthma in particular is continually increasing is a matter of record. From recent unanimous global statistics or, if limited to Italy, from the recent report of Serafini and Di Nardo (presented to the Second World Congress of Allergology held in Paris in 1959), we learn that the mortality due to bronchial asthma tripled between 1924 and 1954, both in terms of absolute figures and in percentages related to the entire population.

We shall not, in this paper, concern ourselves with an analysis of the causes of this increase. Nevertheless, without consideration of any increase that is only apparent and for which improved diagnostic methods are mainly responsible, it is certain that the larger number of asthma cases is related to the introduction and diffusion of substances possessing antigenic action. Among these agents we include castor beans, which, because of their high nitrogen content, are being utilized to an ever increasing extent in the production of agricultural fertilizer mixtures.

Aside from the above considerations, these allergic manifestations are of great interest because of the following fundamental aspects:

1. The gravity of the asthma attack precipitated by this allergen. The literature refers to fatal cases.

2. The possibility of simultaneous occurrence of symptoms in several members of the same family unit, in workers engaged in the same work (as we, ourselves, have noted, and which we will discuss later), or in even larger population groups inhabiting the same circumscribed area.

Ordman (1957) described the sudden appearance of some 200 cases of asthma in a coastal city in South Africa among workers of a plant engaged in the extraction of oil from castor beans, among farmers using the compressed castor beans for fertilizer, and among residents living in the vicinity of this plant. The diagnoses were confirmed by the positivity of cutaneous ricinus sensitization tests and by the periodic nature of the asthmatic manifestations, which occurred exclusively during the work cycles. These high, simultaneous incidences of asthma are of great significance, especially when one considers the rarity of this disease in South Africa.

Analogous observations were made by Mendes, who described 150 cases of asthma, 9 of them fatal, in the Brazilian city of Bauru, in the vicinity of a castor-seed pressing plant.

Recently, Panzani called attention to the danger of ricinus sensitization of persons living in the vicinity of ricinus-processing plants and of agricultural workers using the pressed seeds for fertilizer. Panzani observed about 100 cases in the city of Marseille, some of whom were severely ill.

3. The possibility that sensitization and precipitation of attacks may occur as a result of transitory and sporadic contacts that easily elude the anamnestic inquiry and thus render diagnosis difficult, as in the case of a bank employee living in a small city near Bologna; the case of a young student who was sensitized by her fiance, director of a ricinus-processing plant; and the case of a domestic worker who became sensitized through her father who had been in frequent contact with fertilizers containing castor beans.

Brief Considerations Regarding Castor Seeds

The ricinus plant belongs to the group of Euphorbiaceae. It is widely cultivated in India, the United States, Africa, Manchuria, and Brazil. From the seeds is extracted the oil, which has many uses in industry and a limited use in pharmacology. After extraction of the oil, which may be accomplished with simple mechanical presses or by chemical solvents, the remaining dross is used in the production of fertilizers because of its high nitrogen content.

In this dross are two substances of basic pharmacological importance: the poison toxalbumin, which can be lethal to man in doses of 0.035 milligram, and a substance of high antigenic potency that, according to Spiess, is also present in the leaves.

Originally Allilaire thought the allergen was identical with the toxalbumin; later, however, the existence of two distinct fractions, one toxic and the other allergenic, was discovered. The latter was denoted by the term "ricino-allergen"; it is water-soluble, dialyzable, and heat resistant. This discovery is of the highest importance. More recently the sensitizing fraction was found to be represented by a protein-polysaccharide complex that, even when deprived of the polysaccharide, retains its extremely high antigenic potency. Thus, we are confronted with the peculiar phenomenon of finding in the same seed two substances, one with toxic action and the other with an antigenic activity of very high pharmaco-biological potency.

The anaphylactic action of the agent has been noted together with the extreme facility with which guinea pigs may be sensitized by it. We have carried out such sensitizations by means of microdoses (0.1 cubic centimeter of a 6-percent solution administered intraperitoneally at 2-day intervals) and by shocking the animals with aerosols, thereby causing fatal anaphylactic shocks.

Our antigen was prepared according to Clarke's method, which gives an extremely active antigen totally free of toxic action, a condition that we were not able to attain with the same degree of certainty with other methods of preparation. In fact, with some of our other preparations we obtained negative results; in particular we recall the case of a patient in whom, by means of a superficial scarification, we produced a process of cutaneous eschar with lypmhadenoid satellite, exactly as described as resulting from microdoses of toxin acting through the skin.

Personal Observations

Our personal observations may be divided into two groups: the first group of observations was of a certain number of patients who came voluntarily to our clinic (the Antiallergic Ambulatorium of the Medical Clinic) or who were hospitalized at that institution; the second group of observations was carried out in a plant near Ancona engaged in pressing out the oil of castor beans where tests were made to acquire a better understanding of the pathogenesis of ricinus asthma and of the possibilities of allergization by this allergen.

It would require an excessive amount of space to present in detail each individual case; we feel it would be preferable to discuss them collectively and, at the same time, emphasize the special characteristics, if any, of individual cases.

Our cases numbered about ten, admittedly a rather small number, representing 7 per 1,000 of the 1,500 asthmatics whom we studied between 1953 and 1958. In reality, however, the number of patients whom we treated for ricinus allergopathy was much higher, but we prefer for the sake of statistical accuracy to consider here only those cases who had presented themselves voluntarily at our out-patient clinic or hospital.

Of the ten, seven were farmers; one, a bank employee; one, a student (female); and one, a young homemaker.

The clinical histories of the seven farmers are almost identical: in all seven, sudden severe—at times extremely violent—crises of asthma occurred, preceded by a rhinitic (in some cases oculo-rhinitic) symptomology while in contact with fertilizer mixtures. One member of this group attended to the unloading of trucks carrying sacks of fertilizers, while the others were engaged in the spreading of the same material in the furrows.

The subsequent course of the illness, too, was analogous in all seven patients. Following the asthma attacks, they were immediately removed from their work; after treatment with symptomatic drugs, they improved rapidly. Only in two cases were the asthma attacks so violent that the patients required hospitalization.

Whether hospitalized or only removed from their work and treated with symptomatics, the seven farmers surmounted the crises. During the next 48 hours all of them showed significant improvement, particularly marked in those patients who continued to stay away from work or who were hospitalized.

On returning home from the hospital and resuming their previous activities, they suffered new asthmatic crises, which, this time, were even more violent. In some cases this alternation between interruption of work and well-being on one hand and returning to work and new crises on the other hand, recurred three or four times. Some of the patients had to be rehospitalized two or three times for brief periods; some of them were transferred to the Medical Clinic of Bologna; and others were seen by us in the ambulatorium.

The hospitalized patients showed a characteristic immediate improvement so that after 24 to 48 hours they were clinically negative, with full restitution of their respiratory functions.

In regard to these patients, we were confronted with diagnostic difficulties. In fact, although treatment was soon oriented toward the suspicion of an asthmatic crisis caused by an exogenous allergen (it may be recalled how almost all asthmatics, of other types also, always tend to improve once they are hospitalized, even when treated only with placebos), we could not at first elicit the nature of the allergen involved, since castor-bean powder did not form part of our collection of allergens (and we have since found out that it is missing also from other collections).

When, however, we established a definite connection between contact with chemical fertilizers and asthma and found that these fertilizers contained briquettes of castor bean, the diagnosis task was greatly facilitated. The diagnosis was subsequently confirmed by the intense positivity of cutaneous tests and the detection, by the method of Prausnitz-Küstner, of constantly circulating antibodies.

On the basis of this initial observation, the subsequent diagnoses were relatively easy and were almost always made in the ambulatorium.

We decided to carry out a study of the entire family of one of the farmers. In fact, having learned that nine members of the family of one of our patients were involved in the same kind of work, we were interested in finding out whether any of these other members had complained of allergic manifestations. Our suspicions were confirmed. Although four members were completely free of any asthmatic attacks, we found, in addition to the patient hospitalized for a very severe crisis, a second member of the family suffering from a more attenuated form of asthma; a third, whose asthma attacks were even milder; and two others who had oculo-rhinitis. The cutaneous tests showed in all patients the existence of a sufficiently clear relationship between positivity and asthma attacks and between the intensity of positivity and the intensity of the symptomology. In those who were free from asthma attacks, the tests were negative. The same results were obtained in the Prausnitz-Küstner passive transfer tests carried out in all these persons.

Among members of this family (who live under the same environmental conditions, belong genetically to the same stock, and work in nearly identical conditions in contact with the same antigen), some are highly sensitized, some less highly sensitized, and some are not sensitized at all. This finding led us to attempt a thorough examination of the various family members in order to discover the characteristics that differentiate them from one another.

Frankly speaking, the results were negative. We searched for the existence of dental foci and otorhinolaryngeal changes; we subjecetd our patients to hematological analyses—but all this to no avail. Nor did fractionation of the protein constituents of the blood place in evidence any significant variations in the individual members of the family.

This, then, was what we found in regard to our group of farmers. It is to be noted that these patients displayed neither a familial nor an individual sensitization to other allergic illnesses.

Another of our patients was a worker who came to us because of disturbances of a rhinitic character that occurred during periods when he worked, but whose symptoms became attenuated to the point of actual disappearance during holidays. Anamnesis revealed that he worked in a pharmaceutical laboratory where ricinus seeds were handled. Diagnosis was easy and was subsequently confirmed by cutaneous tests.

Among our patients was a bank employee whose case has many interesting aspects since it demonstrates the possibility of allergization through sporadic and indirect contacts.

This patient had an obvious form of hereditary allergization, both on his father's and his mother's side. Anamnesis revealed that once, when a child, with his father, he entered a shop specializing in chemical fertilizers and was suddenly seized by an attack of thoracic constriction, difficulty in breathing, and—it seems—a state of collapse, for which he was taken to the nearest hospital and treated with adrenalin. Thereupon he quickly recovered.

The patient had almost forgotten this incident. Four years later when passing by a chemical fertilizer shop, he was again seized by a sense of oppression, thoracic constriction, and respiratory difficulties.

The patient did not concern himself with these symptoms. Nevertheless, a few days later he told us that occasionally he would have similar sensations of respiratory constriction accompanied by wheezing and at times by a true state of asthma, even when he was working in his office, in fact, *only* when he was in his office, these attacks occurring very irregularly without any relationship to the climate or season.

When he was first seen in the clinic, he displayed a positive reaction to ricinus.

Later we were able to ascertain that the attacks of asthma occurred when the patient, a cashier at the bank, was approached by an employee of the Agrarian Consortium who was frequently in contact with castor seeds in the course of his work.

In a similar manner we also confirmed the diagnosis of a girl student from Ancona who had come to our ambulatory complaining of crises of asthma when in the company of her fiance. Aware of the existence of psychogenic asthma and conditional reflexes, we were inclined, when the patient first told us about her symptoms, to approach them by the latter route. After cutaneous tests showed an intensive positive reaction to castor seeds and we learned that the fiance was director of a ricinus-processing plant, we felt justified in diagnosing the case as ricinus asthma and attributing the sensitization to residues of this antigen attached to the fiance's clothing. This patient also had a hereditary allergic sensitivity.

Very similar to the above described case of indirect sensitization is that of a young homemaker who came to us recently complaining of asthmatic attacks accompanied by rhinitic symptoms. She had an intensive positive reaction to ricinus, and her sporadic attacks were clearly related to the occupation of her father, a handyman, who periodically came in contact with castor seeds.

To clarify the pathogenic mechanism of this sensitization, we also studied a group of workers attached to a plant where castor beans were processed into fertilizer briquettes and castor oil by extraction. Castor oil was extracted by pressing the beans; the residue was pulverized, compressed into disks, and dried. The phase of the operation particularly noxious from the point of view of provoking respiratory symptoms was the pulverizing of the seeds.

The 17 workers examined by us were subjected to anamnestic inquiries, objective tests, cutaneous reactions with castor extract, and investigation of the circulating antibodies according to Prausnitz-Küstner.

The results showed the absence of prior allergies, and the existence, in 15 out of 17 patients, of a symptomology that ranged from a simple sensation of nasal obstruction of the rhinitic type often associated with ocular manifestations (of oculo-rhinitic character), through mild respiratory difficulties, to true asthmatic attacks closely related to the atmosphere of the place of work.

In some of the patients, these disturbances occurred every time and only when they were exposed to the working environment; in other patients the onsets of the attacks were much less regular. The symptoms were influenced by changes in atmospheric conditions and above all by sudden temperature changes.

The connection between the gravity of the symptomology and the length of contact with castor-bean powder is illustrated in the grave nature of the symptoms encountered in workers taking part in the pulverizing operation and pressing of the briquettes and the absence of symptoms in workers such as the porter and watchman who were not in direct contact with the operational cycle of castor-bean processing.

The cutaneous tests were positive in 16 out of 17 workers; only the watchman showed a negative reaction.

We then conducted a biological evaluation of the sensitivity by injecting intradermally extremely diluted solutions of ricinus at five different concentrations, beginning with the lowest concentration and going up the scale until the first signs of positive reaction were noted.

The experiment was undertaken to classify our subjects according to degree of sensitization, which would then be related to the number of years worked at the plant. The tabulated results show a very definite relationship between degree of sensitization and length of employment.

This investigation has shown that all persons in a group in intimate contact with castor beans can become sensitized and that the gravity of the symptomology parallels the degree of intensity of contact with the incriminating antigen and is reflected in the corresponding intensity of positivity of the cutaneous tests.

In conclusion, our experience shows that ricinus asthma is a rather rare illness, amounting to 7 per 1,000 of the 1,500 cases of asthma we studied during the past 5 years, and that the illness may strike any category of persons but is most prevalent among agricultural laborers and workers in contact with castor beans.

The pathological picture presented by the disease is such that neither its symptomology nor the objective findings reveal anything particular that could point to a specific diagnosis. In fact, the physician encounters crises of asthma with impressive functional emphysema, scarce coughing, and a thoracic semeiological evidence of bronchial obstruction with scarce endobronchial exudation, a syndrome encountered in asthmas attributable to a wide variety of inhaled substances.

From the diagnostic point of view, the gravity of attacks particularly ought to be evaluated, since in its exogenic forms the attack is common only to a limited number of allergies. Among these are the pollen of Parietaria, which is distinguished by the seasonal nature of its diffusion; penicillin, which, when inhaled either accidentally or in the course of aerosol treatment, may precipitate the most severe crises of asthma; and the scurf of animals, which can also cause severe attacks. In our experience, however, the attacks of ricinus asthma are much more severe than those caused by any of the agents just mentioned, a fact that may represent a criterion of suspected diagnosis.

In some cases the diagnosis is easy, as in patients whose anamneses reveal past contacts with ricinus. In others, however, it might be quite difficult, as in the three cases described above in which direct contacts were absent. Although the anamnesis may serve for orientation purposes, the exact etiological diagnosis should always be combined with cutaneous tests, which give very satisfactory answers and should be performed in every case of asthma.

It should be remembered that one must administer these tests with caution, always starting with solutions of the highest dilution (1:10,000,000 for the puncture test) and, only when the result is negative, proceeding to the next highest concentration and eventually to intradermic injections. We insist on this precaution because we have observed cases of severe shock caused by doses, even microdoses, administered intradermally.

Our investigation at the plant revealed that nearly the entire labor force had complained for some time of mild and more or less evident clinical signs of ricinus sensitization and that the degree of sensitization was roughly proportional to the number of years of activity in the factory. Even the increase or decrease in the intensity of symptoms was related to the length of exposure to the allergen.

From the etiopathological point of view, we may state that in ricinus asthma both sensitization and precipitation of attacks proceed via the inhalatory route.

There also exist dermatoses caused by direct contact and sensitizations by ingestion, but these modalities are not commonly utilized by asthma.

The most interesting aspect of the pathogeneses of these forms is the very high allergizing potency of castor seed, which seems to dominate completely the process of sensitization. Normally one assumes that allergic asthma strikes persons who possess an elective tendency toward self-sensitization, attributing, so to speak, a fundamental value to the individual constitution, which, among its most constant characteristics, normally comprises a familial hereditary sensitivity. From our observations, however, we could classify the stricken individuals into two groups:

1. The first group is characterized by sporadic outbreaks of allergic manifestations in individuals, generally with a familial or personal allergic disposition, in whom the allergizing action of the seed (with which they hardly come into contact) is evidently associated in the creation of the allergic state with a particular individual disposition to being sensitized.

2. The second group, which differs sharply in modality of onset from the first and which comprises the majority of our observed cases, is characterized by an outbreak of allergic manifestations in groups or families or collectives (in close contact with the allergen) in a manner resembling the outbreak of an epidemic of infectious disease. In this event there probably exist, besides the allergen, cofactors of an atmospheric nature (temperature or humidity) that potentiate the allergizing action of the antigen and presumably facilitate the latter's absorption. There remains, nevertheless, the consideration that in these cases the allergopathy does not seem to be an exclusive affection of some subjects specifically characterized by their anomalous reactive capacity, but an affection that develops in the organism under the influence of exogenous factors.

How are we to reconcile pathogenetically these two divergent forms of behavior? We are in the realm of hypotheses: it is probable that to acquire a pathological sensitization, we must first overcome a certain threshold erected across the inversely proportional sum of allergizing and individual factors, as may be seen from the scheme we have projected. In this way one could, perhaps, explain the sensitization of the bank employee, who was constitutionally allergizable even by sporadic and irregular contacts with castor beans, and the sensitization of the group of workers who had no individual family history of allergy, but who remained in close and prolonged contact with the same antigen.